الجمهورية الجزائرية الديمقراطية الشعبية
Democratic and Popular Republic of Algeria
وزارة التعليم العالي والبحث العلمي
Ministry of Higher Education and Scientific Research
جامعة سعيدة الدكتور مولاي الطاهر
University of Saida Dr. MOULAY Tahar

كلية علوم الطبيعة والحياة
N° d'Ordre
Faculty of Natural and Life Sciences
قسم البيولوجيا
Department of Biology

Thesis Presented for obtaining the MASTER diploma

In Biological Sciences

Specialty: Applied Biochemistry

Title

The Bi-Directional Relationship Between Sarcopenia And Type 2 Diabetes

Presented by:

- Mss : NAAR Ilhem

Sustained : 23 June 2025

Before the jury composed of:

Supervisor	Mr. KEBIR Nasr eddine	Dr MCA UMTS University
President	Mr. Yahia BELLIL	Dr UMTS University
Examiner	Mr. Adli Djallal Eddine Houari	Pr UMTS University
Examiner	Mm. Chahrour Wassila	Dr MCA UMTS University

Academic year 2024/2025

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Dedications

To My Heart, My Home

To my mother…..To her heart,….To her spirit….gentle yet unshakable,

For her smile,

For her eyes that lit my world.

To the one who gave me the strength to dream,

The one who shaped Who I've become

May you always be safe,

To those who saw a light in me

when I was still learning to see it myself.

To all who truly believed in me.

To my big sister *Siham*,

Who wrapped me in her warmth,

In her unwavering support.

To my dearest friends,

My most cherished ones *Ghadir, Fatima, Aya*

your loyalty is louder than storms.

And lastly,

to me —

the girl who stayed.

The girl who rose,

even when doubt clung to her sleeves.

You've come this far.

You've earned your name.

Acknowledgement

First and foremost, I thank God Almighty for granting me the strength, patience, and perseverance to complete this work. Without His guidance and mercy, none of this would have been possible.

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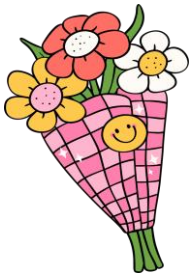

List of abbreviations

AA	Amino Acids
AGE(s)	Advanced Glycation End Product(s)
Akt	Protein Kinase B
AMPK	AMP-Activated Protein Kinase
ATF4	Activating Transcription Factor 4
BAIBA	β-Aminoisobutyric Acid
BAX	Bcl-2 Associated X Protein
BMI	Body Mass Index
C/EBPβ	CCAAT/Enhancer-Binding Protein Beta
CK	Creatine Kinase
CNS	Central Nervous System
CSA	Cross-Sectional Area
Cyt c	Cytochrome c
DC	Dendritic Cells
DII	Dietary Inflammatory Index
DM	Diabetes Mellitus
DXA	Dual-energy X-ray Absorptiometry
eIF2α	Eukaryotic Initiation Factor 2 Alpha
eIF4E	Eukaryotic Initiation Factor 4E
EPA	Eicosapentaenoic Acid
FFA	Free Fatty Acids
FoxO	Forkhead Box O
G6P	Glucose-6-Phosphate
GC	Glucocorticoids
GLUT4	Glucose Transporter Type 4
HFD	High-Fat Diet
HOMA-IR	Homeostasis Model Assessment for Insulin Resistance

HPA	Hypothalamic-Pituitary-Adrenal
IGF-1	Insulin-like Growth Factor 1
IL-6	Interleukin-6
IκB	Inhibitor of NF-κB
IMF	Intramuscular Fat
IMAT	Intermuscular Adipose Tissue
IR	Insulin Resistance
IRS	Insulin Receptor Substrate
LMM	Low Muscle Mass
MRI	Magnetic Resonance Imaging
mTOR	Mammalian Target of Rapamycin
MUFA	Monounsaturated Fatty Acids
MuRF1	Muscle RING-Finger Protein-1
NF-κB	Nuclear Factor Kappa B
PA	Physical Activity
PI3K	Phosphatidylinositol 3-Kinase
PKB	Protein Kinase B
POMC	Proopiomelanocortin
PUFA	Polyunsaturated Fatty Acids
RONS	Reactive Oxygen and Nitrogen Species
ROS	Reactive Oxygen Species
SCAT	Subcutaneous Adipose Tissue
SFA	Saturated Fatty Acids
SREBP1	Sterol Regulatory Element-Binding Protein 1
T2DM	Type 2 Diabetes Mellitus
TAZ	Transcriptional Coactivator with PDZ-binding Motif
TNF-α	Tumor Necrosis Factor Alpha
TRAF6	TNF Receptor Associated Factor 6

UPS	Ubiquitin–Proteasome System
VO_2 max	Maximal Oxygen Consumption
WAT	White Adipose Tissue
YAP	Yes-associated Protein

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Abstract

Sarcopenia, a progressive loss of skeletal muscle mass, strength, and function, is increasingly recognized as a significant comorbidity in individuals with type 2 diabetes mellitus (T2DM), with both conditions sharing overlapping pathophysiological mechanisms such as insulin resistance, chronic inflammation, oxidative stress, mitochondrial dysfunction, and hormonal imbalance. This cross-sectional study involving 200 T2DM patients from Saïda, Algeria, investigated the bidirectional relationship between T2DM and sarcopenia, focusing on clinical, functional, and metabolic parameters.

Results revealed that 95% of participants were unaware of sarcopenia, and 82% did not understand the importance of muscle strengthening in diabetes management. Alarmingly, 64% reported no physical activity, and 55% had inadequate or uncertain protein intake. Functional impairments were common: 31% struggled with lifting 5 kg objects, and among patients with over 10 years of T2DM, 56.2% reported stair-climbing difficulties. Muscle decline was observed even in patients under 40 years, with 42.1% reporting significant loss. Poor glycemic control (HbA1c >8%) was strongly associated with decreased muscle strength. Comparative analysis showed that diabetic patients exhibited reduced muscle mass indices and higher intramuscular fat accumulation compared to nondiabetic individuals. Sarcopenic obesity further exacerbated metabolic dysfunction.

A significant negative correlation between skeletal muscle mass and insulin resistance markers reinforces the central role of muscle in glycemic regulation. These findings confirm a self-reinforcing cycle between sarcopenia and T2DM, underlining the urgent need for integrated strategies—targeting nutrition, physical activity, and metabolic control—to disrupt this cycle and improve patient outcomes.

Keywords: Sarcopenia, Type 2 diabetes mellitus, Insulin resistance, Muscle atrophy, Inflammation, Mitochondrial dysfunction, Sarcopenic obesity

الملخص

السـاركوبينيا، وهـي فقـدان تـدريجي فـي كتلـة العضـلات الهيكليـة وقوتهـا ووظيفتهـا، تُعـدّ بشـكل متزايـد مرَضًـا مرافقًـا هامًـا لـدى الأفـراد المصـابين بـداء السـكري مـن النـوع الثـاني(T2DM) ، حيـث يشـترك المرضـان فـي آليـات فسـيولوجية مرضـية متداخلـة مثـل مقاومـة الإنسـولين، الالتهـاب المـزمن، الإجهـاد التأكسـدي، خلـل الميتوكوندريا، واختلال التوازن الهرموني.

هـدفت هـذه الدراسـة المقطعيـة التـي شـملت 200 مريضًـا مصـابًا بالسـكري مـن النـوع الثـاني مـن مدينـة سـعيدة بـالجزائر إلـى دراسـة العلاقـة الثنائيـة الاتجـاه بـين السـكري والسـاركوبينيا، مـع التركيـز علـى المؤشـرات السريرية والوظيفية والتمثيل الغذائي.

أظهـرت النتـائج أن 95% مـن المشـاركين لـم يكونـوا علـى درايـة بالسـاركوبينيا، و82% لـم يـدركوا أهميـة تقويـة العضـلات فـي إدارة مـرض السـكري. والمقلـق أن 64% أقـروا بعـدم ممارسـة أي نشـاط بـدني، و55% لـم يكـن لـديهم مـدخول كـافٍ أو مؤكـد مـن البـروتين. كمـا كانـت الاضـطرابات الوظيفيـة شـائعة، إذ أبلـغ 31% عـن صـعوبة فـي رفـع أشـياء تـزن 5 كـغ، ومـن بـين المرضـى المصـابين منـذ أكثـر مـن 10 سـنوات، أفـاد 56.2% بوجود صعوبات في صعود السلالم.

وقـد لـوحظ تـدهور عضـلي حتـى لـدى المرضـى الـذين تقـل أعمـارهم عـن 40 عامًـا، حيـث أبلـغ 42.1% عـن فقـدان عضـلي كبيـر. كمـا تبـيّن أن ضـعف الـتحكم فـي نسـبة السـكر فـي الـدم (HbA1c > 8%) مـرتبط بشكل قوي بانخفاض قوة العضلات.

أظهـرت التحلـيلات المقارنـة أن مرضـى السـكري لـديهم مؤشـرات كتلـة عضـلية أقـل وتـراكم أكبـر للدهون داخل العضلات مقارنة بغير المصابين. كما فاقمت السمنة الساركوبينية من سوء الحالة الاستقلابية.

وارتبطـت الكتلـة العضـلية الهيكليـة سـلبًا وبشـكل ملحـوظ مـع مؤشـرات مقاومـة الإنسـولين، ممـا يعـزز الـدور المحـوري للعضـلات فـي تنظـيم نسـبة السـكر فـي الـدم. وتؤكـد هـذه النتـائج وجـود حلقـة مفرغـة بـين السـاركوبينيا والسـكري مـن النـوع الثـاني، ممـا يسـتدعي الحاجـة الماسّـة إلـى اعتمـاد اسـتراتيجيات متكاملـة تستهدف التغذية، النشاط البدني، والتحكم الاستقلابي لكسر هذه الحلقة وتحسين نتائج المرضى.

الكلمات المفتاحية: الساركوبينيا، داء السكري من النوع الثاني، مقاومة الإنسولين، ضمور العضلات، الالتهاب، خلل الميتوكوندريا، السمنة الساركوبينية.

Résumé

La sarcopénie, une perte progressive de la masse musculaire squelettique, de la force et de la fonction, est de plus en plus reconnue comme une comorbidité significative chez les personnes atteintes de diabète de type 2 (DT2), les deux affections partageant des mécanismes physiopathologiques communs tels que la résistance à l'insuline, l'inflammation chronique, le stress oxydatif, le dysfonctionnement mitochondrial et les déséquilibres hormonaux.

Cette étude transversale menée auprès de 200 patients diabétiques de type 2 à Saïda, en Algérie, a examiné la relation bidirectionnelle entre le DT2 et la sarcopénie, en se concentrant sur des paramètres cliniques, fonctionnels et métaboliques.

Les résultats ont révélé que 95 % des participants ignoraient la sarcopénie, et 82 % ne comprenaient pas l'importance du renforcement musculaire dans la gestion du diabète. De manière préoccupante, 64 % ont déclaré ne pratiquer aucune activité physique, et 55 % avaient un apport en protéines insuffisant ou incertain. Les troubles fonctionnels étaient fréquents : 31 % avaient des difficultés à soulever des objets de 5 kg, et chez les patients diabétiques depuis plus de 10 ans, 56,2 % ont signalé des difficultés à monter les escaliers. Une fonte musculaire a été observée même chez les patients de moins de 40 ans, avec 42,1 % signalant une perte musculaire significative. Un mauvais contrôle glycémique (HbA1c > 8 %) était fortement associé à une diminution de la force musculaire.

L'analyse comparative a montré que les patients diabétiques présentaient des indices de masse musculaire réduits et une accumulation de graisse intramusculaire plus importante que les personnes non diabétiques. L'obésité sarcopénique aggravait encore davantage les dysfonctionnements métaboliques.

Une corrélation négative significative entre la masse musculaire squelettique et les marqueurs de la résistance à l'insuline renforce le rôle central du muscle dans la régulation glycémique. Ces résultats confirment un cycle auto-entretenu entre sarcopénie et DT2, soulignant la nécessité urgente de stratégies intégrées ciblant la nutrition, l'activité physique et le contrôle métabolique pour briser ce cycle et améliorer les résultats cliniques.

Mots-clés : Sarcopénie, Diabète de type 2, Résistance à l'insuline, Atrophie musculaire, Inflammation, Dysfonctionnement mitochondrial, Obésité sarcopénique.

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Part I: introduction

Introduction

Sarcopenia is a progressive skeletal muscle disorder characterized by a decline in muscle mass, strength, and function, which increases the risk of adverse outcomes such as falls, fractures, disability, and mortality [1], [2]. While initially recognized as an age-related condition affecting older adults, its relevance has broadened to include populations with chronic diseases, notably type 2 diabetes mellitus (T2DM) [1], [3]. The definition of sarcopenia has evolved over time, shifting from a sole focus on muscle mass to a more comprehensive approach that incorporates strength and physical performance as key components [1], [2], [4]. Various international groups, including the European Working Group on Sarcopenia in Older People (EWGSOP) and the Foundation for the National Institutes of Health (FNIH), have proposed diagnostic criteria; however, a universal standard remains elusive [4]. Despite its significance, sarcopenia is often underdiagnosed and undertreated in clinical settings [1].

The condition stems from a multitude of factors, including aging, physical inactivity, hormonal shifts, chronic inflammation, insulin resistance, poor nutrition, and coexisting diseases such as T2DM [3]. The bidirectional relationship between sarcopenia and T2DM, which has garnered considerable research interest, is further underscored by this overlap with metabolic disorders [3]. Recent findings indicate that sarcopenia and type 2 diabetes mellitus (T2DM) do not merely coexist, but rather interact in a complex bidirectional manner, where each condition exacerbates the other through shared metabolic and inflammatory pathways.

Exploring this connection may inform strategies to prevent and manage both conditions, ultimately enhancing health outcomes and quality of life. Prevalence estimates for sarcopenia range from 5% to 13% among adults aged 60 and older, escalating to 50% or more in those over 80 [9], [10]. The burden of sarcopenia is particularly pronounced in rapidly aging regions, such as East Asia and Europe [11].

Type II diabetes mellitus (T2DM), responsible for approximately 90% of all diagnosed cases of diabetes [5], [6], is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from insulin resistance (IR)—defined as a diminished cellular response to insulin [5], [6]—and inadequate insulin secretion by pancreatic β-cells, thereby disrupting glucose homeostasis [5], [6]. Typically manifesting in adults over 45 years of age [6], T2DM is increasingly diagnosed in younger individuals, including children and

adolescents [6], driven by obesity, sedentary lifestyles, and high-calorie diets [6], with peak prevalence in aging populations [8]. The condition involves multiple organs, including the pancreas, liver, skeletal muscle, adipose tissue, kidneys, brain, and small intestine [5]. In these organs, visceral fat drives insulin resistance (IR) through inflammation, marked by elevated free fatty acids, adipokine dysregulation [5], and a proinflammatory state with advanced glycation end products (AGEs) and oxidative stress [8]. Additional factors, such as alterations in the gut microbiota and immune system dysfunction, contribute to the progression of this condition [5]. The diagnosis of IR is made on the basis of criteria such as a fasting glucose level of ≥126 mg/dL, a HbA1c level of ≥6.5%, the use of anti-diabetic medication, or a prior diagnosis [7].

Type 2 diabetes mellitus (T2DM) is associated with age-related muscle decline, particularly sarcopenia, which may contribute to the development and exacerbation of the disorder by impeding glucose uptake, reducing metabolic rate, and decreasing activity levels [8]. These effects have been shown to heighten the risk of micro- and macro-vascular complications [8], with cardiovascular disease being the leading cause of morbidity and mortality [5]. According to recent global estimates, between 451 and 463 million adults were affected by T2DM between 2017 and 2019 [5], [8], with projections indicating that this number could reach 700 million by 2045 [5]. The disease imposes a disproportionate burden on low-to-middle-income countries, generating an economic cost of 720 billion USD in 2019 [5]. The public health implications of T2DM are compounded by underdiagnosis, as well as its interactions with comorbidities such as sarcopenia.

A comprehensive investigation into the interplay between sarcopenia and T2DM is imperative for the development of targeted therapeutic and preventive strategies. Given the increasing global prevalence of both conditions, a comprehensive understanding of their interaction could enhance early detection, optimize treatment approaches, and reduce the burden of associated complications, such as cardiovascular disease and disability.

The prevalence of type 2 diabetes mellitus (T2DM) has reached epidemic levels, with 463 million adults (9.3% of the global population) affected in 2019 and an anticipated rise to 700 million by 2045 [12]. The highest rates of T2DM are observed in low- and middle-income countries, driven by urbanization, dietary shifts, and reduced physical activity [14], [15]. Aging, a pivotal risk factor, further links T2DM to sarcopenia, accentuating their shared challenges in aging populations.

The objective of this study is to investigate the mechanisms that underlie the bidirectional relationship between sarcopenia and type 2 diabetes mellitus (T2DM). The investigation will entail an analysis of their shared pathophysiological pathways and a discussion of potential interventions to mitigate their impact.

Part II : Literature Review

II.1. Introduction to Sarcopenia

II.1.1. Background and Historical Context:

The earliest documented observations of age-related muscle loss date back to 1931, when British neurologist Macdonald Critchley described “involutional changes” in the muscles of older adults, noting that “the entire musculature tends with advancing age to undergo involutional changes, which are manifested as wasting”)[1]. He attributed this decline to “the general process of senile atrophy,” reflecting the era’s perspective of muscle loss as an inevitable part of aging rather than a distinct condition [2]. These early observations, though limited by the scientific understanding of the time, laid the groundwork for later research into muscle aging

In the 1970s, Nathan Shock, often regarded as the father of gerontology, advanced the field through the first large-scale longitudinal studies on age-related physiological changes, such as the Baltimore Longitudinal Study of Aging. His research quantified declines in various functions, revealing that muscle mass loss was among the most significant age-related changes [4]

In 1997, Rosenberg, emphasized Shock’s findings, introducing urinary creatinine excretion as a proxy for muscle mass and highlighting its correlation with a declining basal metabolic rate, suggesting that muscle loss might be a more critical aging marker than other physiological declines [1] This period marked a shift toward systematic investigation, setting the stage for a more focused study of muscle decline

Irwin Rosenberg formally introduced the term "sarcopenia" in 1988 during a meeting in Albuquerque, New Mexico, to describe the age-related loss of lean body mass.

By 1995, Evans expanded on this concept, linking sarcopenia to functional impairments such as reduced strength and mobility, which increased the risk of falls and disability among older adults[2].

In 2000, the World Health Organization (WHO) recognized sarcopenia as a significant risk factor for loss of independence and various morbidities in the elderly. It targeted sarcopenia as modifiable with lifestyle changes

II.1.2. Evolution of the Current Definition and Diagnostic Criteria

Sarcopenia is a progressive and generalized skeletal muscle disorder characterized by the accelerated loss of muscle mass and function.[3]

The term "sarcopenia" comes from Greek, combining "sarx" (**flesh**) and "penia" (**loss**). It was first introduced by Irwin Rosenberg in 1988 during a meeting in Albuquerque, New Mexico, aiming to highlight the decline in lean body mass associated with aging.[4]

Initial Definition

The first operational definition of sarcopenia was in 1988 and focused solely on low lean mass as a surrogate measure for identifying the condition. [5] This definition has since evolved to include decreased muscle strength and physical performance, reflecting the multidimensional nature of the disorder.[6]Multiple working groups have proposed diagnostic criteria, but true consensus remains elusive due to varying definitions and standards.:

1. **ESPEN Special Interest Group (SIG) Definition**

The Special Interest Group (SIG) within the European Society for Clinical Nutrition and Metabolism (ESPEN) in 2010 defined sarcopenia as: the loss of muscle mass and strength. Diagnostic criteria included muscle mass (≥2 standard deviations below the mean of young adults) and gait speed (<0.8 m/s). [7]

2. **European Working Group on Sarcopenia in Older People (EWGSOP) Definition**

The EWGSOP proposed a broader definition, requiring both low muscle mass (measured via CT, MRI, DXA, or BIA) and low muscle function (assessed via grip strength, gait speed, or Short Physical Performance Battery [SPPB]) for diagnosis. [6]

3. **International Working Group on Sarcopenia (IWGS) and Society for Sarcopenia, Cachexia and Wasting Disorders (SCWD) Definitions**

In 2011, The IWGS and SCWD focused on low appendicular lean mass (ALM) and gait speed (<1 m/s). The SCWD also considered limited mobility, defined as <400 m in a 6-minute walk test. [8]

4. **Asian Working Group for Sarcopenia (AWGS) Definition**

In 2014, The AWGS adapted criteria for Asian populations, defining sarcopenia with low ALM (via DXA: women <5.4 kg/m², men <7.0 kg/m²) and low grip strength (women <18 kg, men <26 kg).[9]

5. **Foundation for the National Institutes of Health (FNIH) Definition**

The FNIH proposed a more conservative definition, focusing on ALM adjusted for BMI and weakness (grip strength: women <16 kg, men <26 kg).[9]

6. EWGSOP2 Definition

In 2019, The EWGSOP2 emphasized muscle strength as the primary criterion, with low muscle mass confirming the diagnosis and low physical performance indicating severity. [3] Low muscle strength is identified by grip strength (<16 kg for women, <27 kg for men) or a chair stand test (>15 s for five rises). Low muscle mass is confirmed using ALM (women <5.5 kg/m², men <7.0 kg/m² via DXA) or non-adjusted measures (women <15 kg, men <20 kg). Physical performance is assessed via gait speed (≤0.8 m/s), SPPB (≤8 points), Timed Up and Go (TUG) (≥20 s), or a 400 m walk test (≥6 min or non-completion). [3] The SARC-F questionnaire was introduced for screening, assessing strength, walking assistance, and falls[3]

7. Sarcopenia Definitions and Outcomes Consortium (SDOC) Definition

In 2020, The SDOC defined sarcopenia based solely on muscle strength and function (grip strength: women <20 kg, men <35.5 kg; gait speed <0.8 m/s), excluding muscle mass due to its weaker predictive value for outcomes like mobility disability.[6]

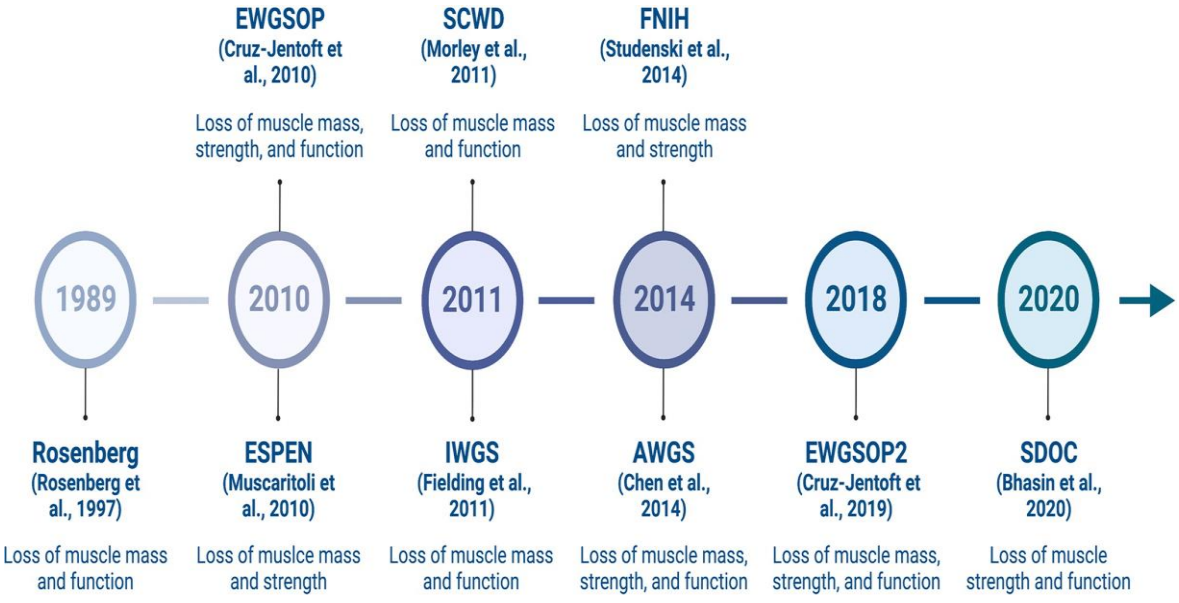

Figure 1 : Timeline of sarcopenia definitions and diagnostic criteria from 1988 to 2020, showing the evolution of criteria across working groups [6]

II.1.3. Epidemiology and Prevalence of Sarcopenia

1. Prevalence and Age-Related Trends

The prevalence of sarcopenia increases significantly with age, reflecting the progressive nature of the condition. In individuals aged 65 to 70 years, prevalence ranges from 5% to 24%. This rises to 11% to 50% in those over 80 years, with some studies reporting rates as high as 53% in this age group.[10], [11] A comprehensive systematic review of 263 studies highlighted the variability in prevalence, ranging from 0.2% to 86.5% depending on the classification used. Meta-analysis estimates showed 10% using the EWGSOP2 definition and 27% using muscle mass-only definitions.[12] Severe sarcopenia, defined by the EWGSOP2 as sarcopenia combined with low physical performance (e.g., slow gait speed), has a prevalence ranging from 2.0% to 9.0% based on 34 studies.[12]

2. Variations by Sex and Setting

Prevalence varies by sex and setting. Men over 75 years show higher rates (58%) than women (45%) in some studies. Prevalence is higher in hospital, post-acute care, or care home settings (23% to 51%) compared to community-dwelling populations (9% to 11%).[12] The evolution of diagnostic criteria significantly impacts these estimates. For instance, the 2010 EWGSOP definition yields a pooled prevalence of 12.9% (95% CI 9.9–15.5), while older muscle mass-only definitions result in higher estimates of 40.4% (95% CI 19.5–61.2). [3] Muscle mass cutoffs have a stronger influence on prevalence than muscle function cutoffs, contributing to the wide heterogeneity across studies. [3], [12] This variability underscores the challenge of studying sarcopenia in populations with Type 2 Diabetes, where consistent diagnostic criteria are needed to assess its true burden.

3. Global Burden and Projections

The global burden of sarcopenia is substantial and growing, driven by an aging population. In 2000, an estimated 600 million people worldwide were aged 60 years or older. This figure is projected to rise to 1.2 billion by 2025 and 2 billion by 2050. [10] Even with conservative prevalence estimates, sarcopenia affects over 50 million people today and is expected to impact more than 200 million in the next 40 years.[10] Incidence data, though sparse, indicate an age-related increase. A study reported an incidence of 1.6% in European men and women aged 40–79 years using the EWGSOP definition, rising to 3.4% in a similar cohort.[3]

4. Sarcopenia in Younger Populations and Understudied Regions

Sarcopenia is not exclusively an aging-related condition. Muscle mass and function decline begin around age 40, yet only 10% of studies in a recent meta-analysis included

individuals younger than 60 years, despite evidence of increased adverse outcomes in middle-aged individuals with sarcopenia. [12] Research on sarcopenia in Africa, where 16% of the world's population (over 1.4 billion) resides, is limited despite poor access to nutrition and healthcare in the region, highlighting a critical need for further study. [12] The lack of data on younger populations and regions like Africa suggests an underestimation of sarcopenia's burden, particularly in populations at risk for Type 2 Diabetes, where early intervention could be beneficial.

5. Health and Economic Consequences

Sarcopenia is associated with significant health and economic consequences. It is linked to frailty, disability, functional decline, increased falls, hospital admissions, and higher rates of morbidity and mortality.[3], [10], [12] Sarcopenic women have 3.6 times higher rates of disability, and men 4.1 times higher, compared to those with greater muscle mass. [11] Severe sarcopenia, particularly when combined with slow gait speed and low grip strength, is an independent risk factor for all-cause mortality, cardiovascular disease, and respiratory disease.

Quality of life is also impaired, as confirmed by systematic reviews using both generic and disease-specific tools. [3] Direct healthcare costs attributable to sarcopenia in the USA were estimated at £18.5 billion in 2000, a figure likely to have increased with the aging population.

Despite its recognition as a disease in the ICD since 2016, few studies have examined prevalence in representative population samples, limiting the external validity of current estimates. [12] The lack of a universal diagnostic criterion complicates efforts to compare results across studies, produce uniform guidelines, and translate findings into clinical practice. The significant health and economic burden of sarcopenia highlights its relevance to Type 2 Diabetes, where shared risk factors like disability and metabolic dysfunction may exacerbate outcomes.

6. Sarcopenic Obesity

Sarcopenic obesity, the coexistence of sarcopenia and obesity, adds complexity to its epidemiology, particularly in relation to metabolic disorders. Using the ASM/height^2 index, prevalence of sarcopenia in obese individuals varies, with studies reporting higher rates in men (10% to 40%) than women (8% to 18%) over 60 years. However, this index may underestimate sarcopenia in overweight or obese individuals due to its correlation with BMI.

Alternative definitions, such as those proposed by Newman et al. and Delmonico et al., use residuals from linear regression models to account for fat mass. Janssen et al. define sarcopenia as an SMI one or two standard deviations below the mean for a younger reference group, reporting a higher prevalence of severe sarcopenic obesity in women.[11] In the New Mexico Aging Process Study, sarcopenic obesity was not associated with a higher incidence of congestive heart disease or hip fractures, but the prevalence of metabolic syndrome was highest in non-sarcopenic obese individuals. In a large sample of Korean adults, sarcopenic obesity defined by the SMI index was significantly associated with metabolic syndrome, with prevalence varying depending on the definition used. A new surrogate index, the muscle-to-fat ratio (MFR, defined as ASM-to-visceral fat area), has been proposed to better assess sarcopenic obesity's impact, showing an independent association with metabolic syndrome and arterial stiffness in a general population. Longitudinal studies are needed to further investigate the effects of sarcopenia and sarcopenic obesity on chronic metabolic disorders and cardiovascular disease, particularly in older individuals.[11]

II.2. Pathophysiology of Sarcopenia

II.2.1. Age-Related Changes in Muscle Tissue:

II.2.1.1. Muscle Fiber Atrophy:

II.2.1.1.1. Skeletal Muscle Structure

Skeletal muscles, ~40% of body weight, consist of multinucleated myofibers organized into fascicles, surrounded by connective tissues: endomysium, perimysium, and epimysium. The sarcolemma (plasma membrane) and satellite cells (for growth/repair) are key, with dystrophin linking actin to the sarcolemma; its absence (e.g., Duchenne dystrophy) causes atrophy. Muscle size depends on myofiber number and size, though pathological infiltration alters this[13]

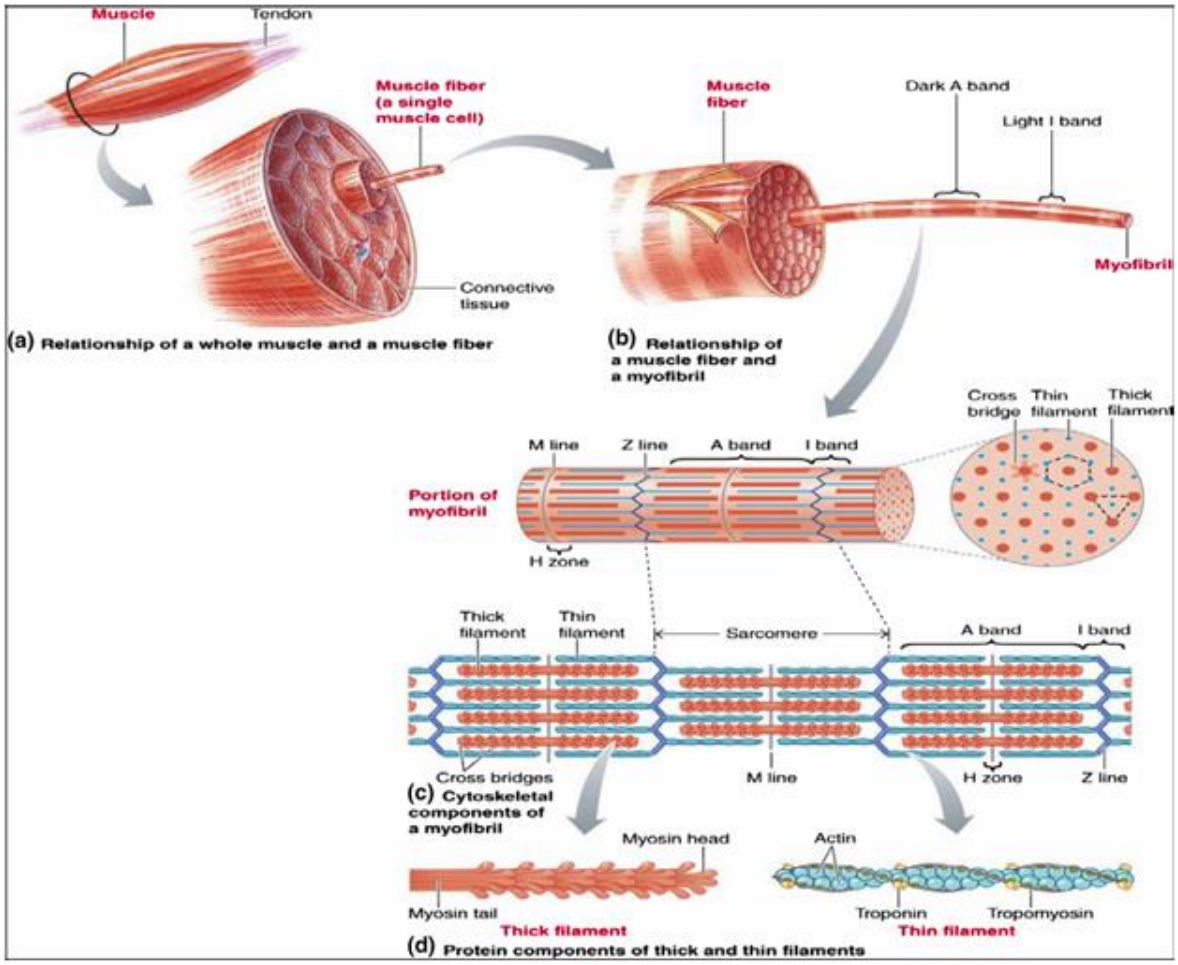

Figure 2 : *Structure of skeletal muscle* [14]

- **Sarcomere and Proteins**

Muscles are striated due to sarcomeres, with thick (myosin) and thin (actin) filaments. Myosin (70–80% with myosin) drive ATP-dependent contraction. Titin and nebulin maintain alignment, while tropomyosin and troponin regulate contraction via calcium. Z discs anchor actin; dysfunctional proteins (e.g., desmin) may cause myopathies [13]. Aging reduces myosin content and modifies cross-bridges, impairing force .[14]

II.2.1.1.2. Muscle Fiber Types and Classification

Skeletal muscle fibers are categorized into three types:

- **Type I (slow oxidative)**: fatigue-resistant, rich in mitochondria.
- **Type IIa (fast oxidative)** : intermediate fatigue resistance.
- **Type IIb (fast glycolytic)**: high power output, quick to fatigue.

Each type expresses specific **myosin heavy chain (MHC) isoforms**, influencing contractile speed and metabolic properties. These fiber types adapt to physiological demands but shift unfavorably with aging, favoring less oxidative, more fatigable profiles.[14]

II.2.1.1.3. Organelles and Energy Metabolism

Myofibers contain T-tubules (signal conduction), sarcoplasmic reticulum (SR, calcium storage/release), and mitochondria (energy production) [13]. Mitochondria support oxidative phosphorylation for endurance; glycolysis fuels short, intense actions [13], [15]. Energy pathways include ATP/CP stores (seconds), glycolysis (minutes), and oxidative phosphorylation (long duration), using glycogen (high intensity) or fatty acids (low intensity) [13]. Aging reduces mitochondrial size/function; exercise can partially reverse this[13], [15]

II.2.1.1.4. Excitation-Contraction Coupling (ECC)

ECC links nerve signals to contraction via SR calcium release. Acetylcholine at the neuromuscular junction depolarizes the sarcolemma and T-tubules, activating dihydropyridine receptors (DHPR) to open ryanodine receptors (RyR1), releasing calcium. Calcium binds troponin C, exposing actin's active sites for myosin cross-bridge formation. SERCA reuptakes calcium, aided by calsequestrin buffering [13]. Aging impairs SR calcium release, reducing ECC efficiency [14].

II.2.1.1.5. Muscle Atrophy and Sarcopenia

Atrophy, the loss of muscle mass/strength, results from protein degradation exceeding synthesis, reducing myofiber diameter [15]. Sarcopenia, age-related atrophy, affects 5–40% of older adults, increasing to 11–50% over 80, with higher prevalence in women and rural areas[14]. It causes mobility issues, falls, and reduced quality of life, impacting >50 million globally. Aging reduces satellite cells (especially type II), SR function, and mitochondria, with men losing more muscle than women. Fiber quality declines due to lower myosin, oxidative modifications, and increased stiffness. Physical activity may preserve strength[14]

- **Primary Atrophy**

Caused by inherited myopathies (e.g., Duchenne, Nemaline), leading to progressive atrophy[15].

- **Secondary Atrophy and Sarcopenia**

Results from aging (sarcopenia), chronic diseases (e.g., cancer, diabetes), immobilization, or malnutrition [15]. Sarcopenia is a major public health issue, driven by multifactorial factors [14].

II.2.1.1.6. Mechanisms leading to skeletal muscle atrophy

Skeletal muscle atrophy results from a complex and incompletely understood interplay of molecular mechanisms disrupting the balance between protein synthesis and degradation Under normal conditions, muscle protein turnover maintains equilibrium through coordinated synthesis and degradation processes. However, atrophy occurs when protein degradation exceeds synthesis, driven by multiple upstream and downstream pathways.[15]

Key upstream triggers include increased oxidative stress, chronic inflammation, and impaired mitochondrial function, which are associated with various disease states and initiate atrophic signaling. Downstream, four primary proteolytic systems contribute to protein breakdown: the ubiquitin-proteasome system, autophagy-lysosome system, caspase system, and calpain system The ubiquitin-proteasome, autophagy-lysosome, and caspase systems degrade substrate proteins completely, acting as "erasers" of protein content. In contrast, the calpain system modulates protein structure and function through limited proteolysis at specific sites, rather than full degradation. These systems interact in a highly regulated, non-independent manner, with complete protein degradation often requiring their combined action [15]

Additionally, the mammalian target of rapamycin (mTOR) signaling pathway plays a critical role in regulating protein synthesis. Downregulation of mTOR activity is a significant contributor to atrophy, as it impairs the muscle’s anabolic response. The intricate regulation and interdependence of these pathways underscore the complexity of muscle atrophy, highlighting the need for further research to elucidate therapeutic targets.[15]

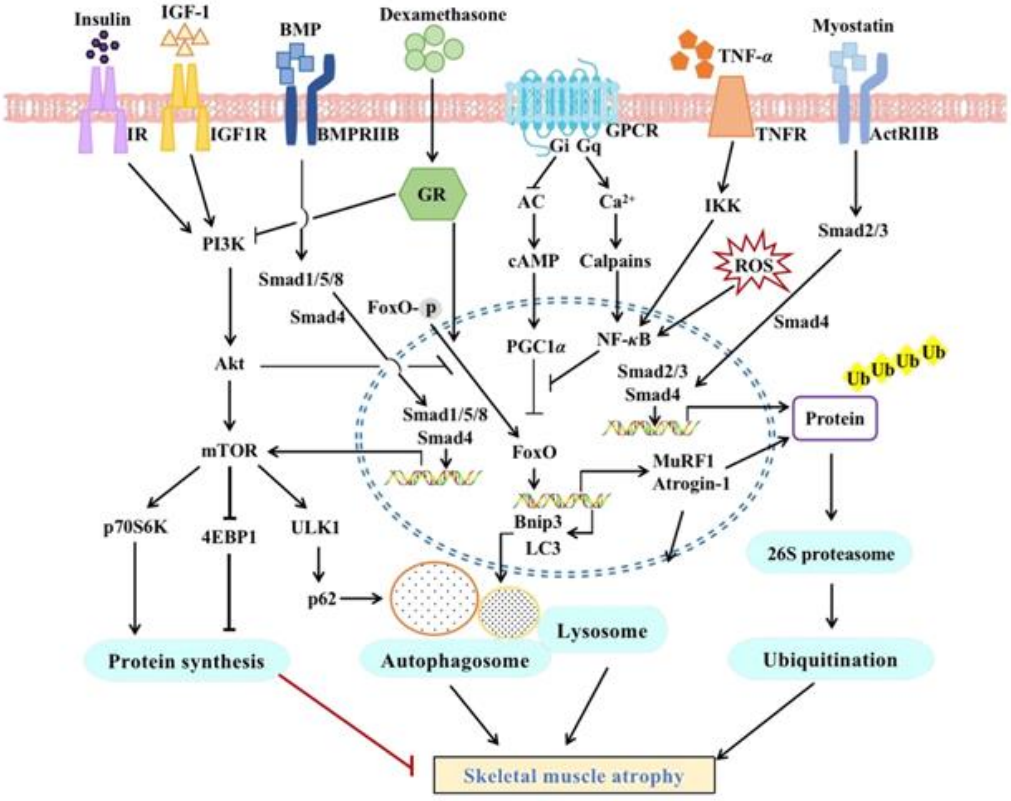

Figure 3 : *Schematic diagram of the signaling pathways associated with skeletal muscle atrophy.*[15]

II.2.1.2. Changes in Muscle Composition:

II.2.1.2.1. Increased intramuscular fat infiltration (myosteatosis).

II.2.1.2.1.1. Definition of Myosteatosis

Myosteatosis refers to the pathological accumulation of fat in skeletal muscle, characterized by an abnormal presence of adipocytes in non-adipose tissue. This ectopic fat depot leads to lipid overload, producing lipotoxic factors such as fatty acids and adipokines, which impair cellular activity, metabolism, and musculoskeletal function [16], [17], [18]. It is distinct from sarcopenia, which involves the loss of muscle mass and function, and is recognized as a separate condition associated with poor metabolic and musculoskeletal health [18].

II.2.1.2.1.2. Types of Fat Infiltration in Skeletal Muscle

Myosteatosis encompasses different adipose depots within skeletal muscle, categorized as follows:

Intermuscular Adipose Tissue (IMAT): Extracellular adipose tissue located beneath the fascia and between muscle groups [17].

Intramuscular Adipose Tissue (IMF): Extracellular adipose tissue found within an individual muscle, situated in the endomysium and perimysium[17], [18].

Intramyocellular Lipids (IMCL): Lipid droplets stored within skeletal muscle fibers [17], [18].

Each type of fat infiltration provides a distinct measure of myosteatosis and may pose unique risks to metabolic and muscle health, particularly in older adults [17].

II.2.1.2.1.3. Cellular Origin of Fat Infiltration in Skeletal Muscle

1. **Myogenic Cells**

Satellite Cells (SCs): In vitro, SCs accumulate lipid droplets under conditions like insulin resistance or low oxygen but do not differentiate into adipocytes; in vivo, lineage tracing shows they are not a primary IMF source

Myf5+ Mesenchymal Stem Cells (MSCs): In vivo, Myf5+ MSCs differentiate into brown adipose tissue (BAT) regulated by Prdm16; in vitro, their role in IMF is limited and not a major contributor [18]

2. **Non-Myogenic Cells**

Fibro-Adipogenic Progenitors (FAPs): In vivo, PDGFRa+ FAPs are the primary IMF source, differentiating into adipocytes during muscle regeneration; in vitro, MME+ FAPs show high adipogenic potential

Fibroblasts: In vitro, TE-7+/CD56- fibroblasts from human skeletal muscle can be induced into adipocytes; in vivo, their role is unclear due to marker overlap with myoblasts

Endothelial Cells (ECs): In vitro, CD34+/CD31+ ECs from adipose tissue differentiate into adipocytes; in vivo, their contribution to IMF is minor but suggested by cell-to-cell communication studies [18]

Side Population Cells (SPs): In vitro, CD34+/Sca-1+/CD45- SPs differentiate into adipocytes; in vivo, these myoendothelial progenitors are located outside muscle fibers but their IMF role is limited

Pericytes: In vitro, NG2+/CD146+ pericytes form lipid droplets in adipogenic media via PPARg2; in vivo, they surround capillaries and may contribute to IMF in specific conditions

PW1+/Pax7- Interstitial Cells (PICs): In vitro, PW1+/Sca-1+ PICs with medium Sca-1 expression show adipogenic potential; in vivo, they overlap with FAPs and pericytes, suggesting a supportive IMF role

Myeloid-Derived Cells: In vitro, subclusters express adipose-related genes (e.g., DLK1, PPARg); in vivo, their regulatory role in fat infiltration is evident but direct IMF contribution remains unclear[18]

II.2.1.2.2. Increased connective tissue and fibrosis.

II.2.1.2.2.1. Extracellular Matrix (ECM) in Skeletal Muscle

II.2.1.2.2.1.1 Definition and Role of ECM

The extracellular matrix (ECM) is a critical component of skeletal muscle, providing a structural framework that supports myofibers, blood capillaries, and nerves, while playing a key role in force transmission, maintenance, and repair of muscle fibers [19]. Excessive ECM accumulation, particularly collagens, leading to fibrosis, impairs muscle function, hinders regeneration after injury, and increases susceptibility to re-injury, being a hallmark of muscular dystrophies, aging, and severe injuries [19]. Understanding ECM mechanisms is vital for advancing knowledge of dystrophic muscle diseases and developing anti-fibrotic therapies[19]

II.2.1.2.2.1.2 Composition of Muscle ECM

- **Collagen Fibrous Networks**: Form the primary structure within an amorphous matrix of hydrated proteoglycans (PG) [19], [20]
- **Collagenous and Non-Collagenous Glycoproteins**: Major protein components supporting ECM integrity[19], [20]
- **Proteoglycans and Glycosaminoglycans (GAGs)**: Contribute to the hydrated matrix, aiding structural flexibility[19], [20]
- **Endomysium**: Thin membrane surrounding each myofiber, rich in collagen types I, III, and V, supports myogenesis and tension conveyance, containing small blood vessels and neurons[19]

- **Perimysium**: Encompasses fascicles, composed of collagen types I and III, transmits force to tendons, and houses larger blood vessels and nerves[19]
- **Epimysium**: Thickest sheath surrounding the entire muscle, primarily collagen type I with minor type III, continuous with tendons, penetrated by major blood vessels and nerves [19],[20]

The ECM constitutes up to 10% of skeletal muscle weight and is essential for locomotor ability, with alterations leading to functional impairments [20]

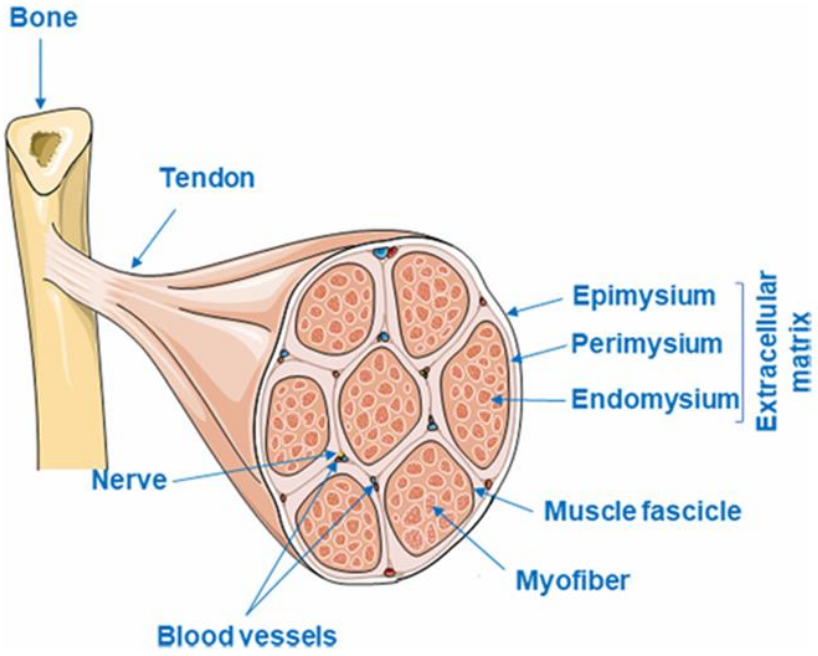

Figure 4 : *Schematic diagram showing the extracellular matrix (ECM) arrangement in skeletal muscle in three levels: the endomysium, perimysium, and epimysium*[19]

II.2.1.2.2.2. Structural Features and Fibrosis

The ECM's collagen network, including perimysial cables (bundles of 25–100 fibrils spanning up to 150 µm), serves as a passive load-bearing structure, though its precise mechanical role remains poorly understood [20]. Nearly all altered-use patterns (e.g., hypertrophy from exercise, atrophy from aging or denervation) result in increased skeletal muscle ECM and fibrosis, contrasting with muscle fiber adaptations, which highlights its sensitivity to environmental changes [20]. Fibrosis, driven by excessive collagen deposition, compromises regeneration and is prevalent in conditions like myopathies and injuries[19], [20]

II.2.1.2.2.3. Key Molecular Factors Regulating Fibrosis in Aging Muscle

TGF-β1: A central profibrotic cytokine that stimulates fibroblasts, ECM production, and myofibroblast differentiation via Smad signaling. [19]

CTGF: A downstream target of TGF-β1 that increases fibrotic proteins (e.g., collagen, fibronectin), independently contributing to fibrosis severity. [19]

Myostatin: Inhibits muscle growth and promotes fibrosis by activating TGF-β1, enhancing fibroblast proliferation and delaying regenerative signaling.

Wnt/β-catenin: Activates fibroblast-to-myofibroblast transformation and boosts collagen gene expression post-injury and in dystrophic muscle. [19]

PDGF: Promotes fibroblast and mesenchymal cell proliferation and differentiation through α and β receptor-mediated pathways. [19]

VEGF: While angiogenic, VEGF also stimulates myofibroblast transformation and ECM deposition, contributing to muscle fibrosis.

FGF: Stimulates fibroblast proliferation and wound healing, with its inhibition reducing fibrosis by lowering collagen expression.

EGF: Enhances fibroblast proliferation, contractility, and fibronectin expression through PKCδ pathway activation.

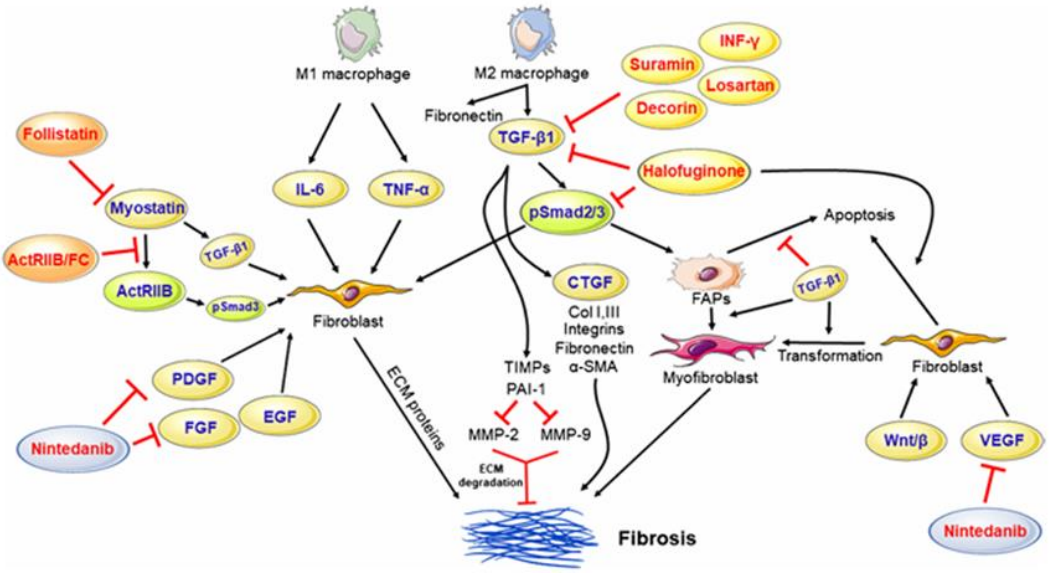

Figure 5 : Schematic diagram showing factors enhancing muscle fibrosis and inhibitors for muscle fibrosis[19]

II.2.1.2.2.4. Definition and Development of Muscle Fibrosis

Muscle fibrosis is characterized by excessive accumulation of extracellular matrix (ECM) components, particularly collagens, due to increased production, reduced degradation, or both, notably affecting the endomysium and perimysium [20], [21]. Following injury, fibrosis develops with inflammation, where neutrophils phagocytose damaged cells, releasing cytokines that recruit monocytes and macrophages, with M1 phenotypes producing proinflammatory cytokines (e.g., TNF-α, IL-6) to activate fibroblasts, and M2 phenotypes releasing TGF-β1 and fibronectin to drive ECM deposition [21]. TGF-β1 activates resident fibroblasts, inhibits FAP apoptosis, and induces their differentiation into fibrogenic cells, while PDGFRβ+ mesenchymal cells transdifferentiate into myofibroblasts via αv integrins, exacerbating fibrosis [21]. This process deteriorates muscle function, hinders regeneration, and increases re-injury risk, commonly seen in muscular dystrophies, aging, and severe injuries[20], [21]

II.2.1.2.2.5. Fibrosis in Dystrophic Muscle via TGF-β Signaling

TGF-β, a potent profibrogenic cytokine with isoforms (TGF-β1, -β2, -β3), is activated via proteolysis and signals through the ALK5/Smad2/3 pathway, translocating to the nucleus to promote transcription, with additional pathways (e.g., Ras/MEK/ERK, p38, JNK) modifying gene expression for myofibroblast differentiation and collagen production [20]. In dystrophic muscle (e.g., DMD, mdx mice), TGF-β induces fibroblast ECM protein

synthesis (e.g., collagen, fibronectin) and reduces degradation enzymes (e.g., collagenase) while increasing TIMPs and PAI-1, fostering fibrosis [20]. Therapeutic agents like decorin, losartan, suramin, and halofuginone inhibit TGF-β signaling, reducing fibrosis and enhancing regeneration, though reversing established fibrosis remains challenging [20]. Myofibroblasts, expressing α-SMA, arise from resident fibroblasts or circulating cells, contributing to chronic fibrotic diseases[20]

II.2.1.2.2.6. Age-Related Fibrosis and Muscle Function

Aged muscle exhibits sarcopenia, marked by muscle mass loss, reduced force, and increased fibrosis, driven by factors like IL-6-induced SC myogenic decline and conversion of SCs/myoblasts to a fibrogenic lineage via Wnt and TGF-β signaling [20], [21]. Wnt/β-catenin upregulation, enhanced by TGF-β2, promotes collagen-producing stromal cell proliferation, while aged fibroblasts show increased TGF-β, collagen IVa2, laminin, and TIMPs, inhibiting ECM degradation [21]. Collagen concentration and stiffness rise with age due to advanced glycation end products, impairing function, with Wnt inhibition reversing fibrogenic conversion [20]. Notch signaling imbalances and factors like ADAM12 and osteopontin further exacerbate fibrosis in aging and dystrophies[20]

II.2.1.3. Motor Unit Remodeling in Sarcopenia

Motor unit remodelling is a critical pathophysiological process in sarcopenia, the age-related loss of muscle mass, strength, and function. As the fundamental units of muscle contraction, motor units (consisting of a motor neuron and the muscle fibres it innervates) undergo significant changes with age, which have been shown to drive muscle atrophy, weakness, and increased fall risk[22]

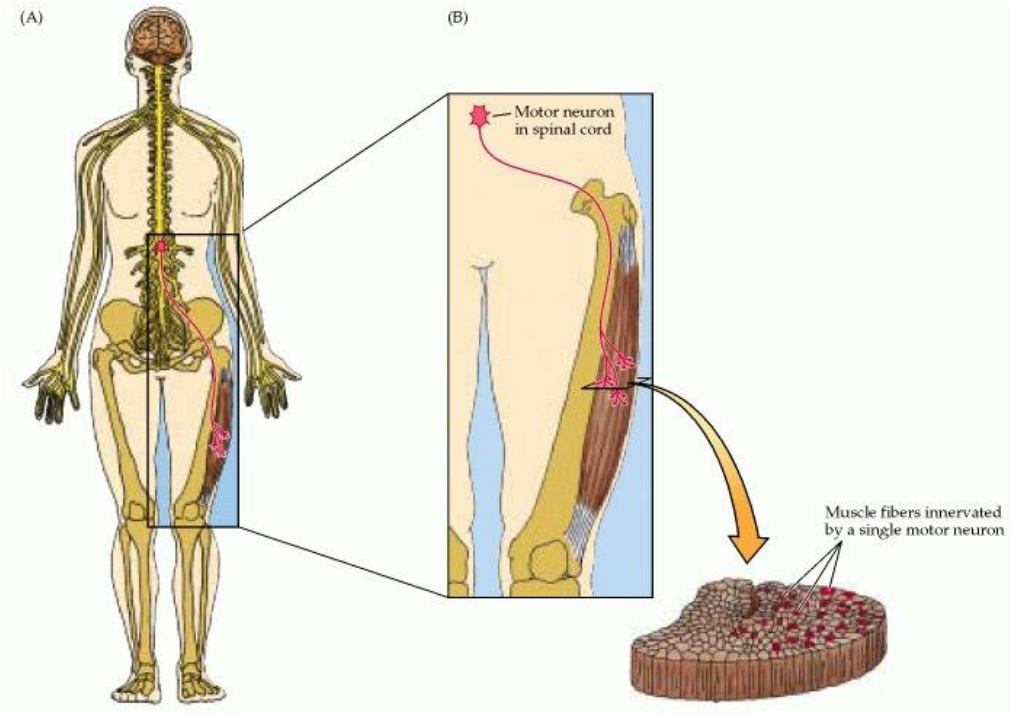

Figure 6 : Diagram of a motor unit showing a lower motor neuron projecting from the spinal cord to multiple muscle fibers it innervates [22]

II.2.1.3.1. The structure of the motor unit and the phenomenon of sarcopenia.

A motor unit is defined as a single motor neuron and all the muscle fibres it innervates, and is thus considered the basic functional unit of the neuromotor system. The size of motor units varies, with innervation ratios ranging from a few fibres in extraocular muscles to thousands in large limb muscles, directly influencing their tension-producing capacity[23].

In sarcopenia, disruptions to motor unit structure compromise muscle function, as the coordinated interaction between motor neurons and muscle fibres is impaired. The recruitment of motor units is determined by the size of the motor neuron (with smaller neurons activated first) and the force capability (with smaller units recruited first)[23]. This process becomes dysregulated in aged muscle. Despite the paucity of data on motor unit morphology, their architectural design exerts a substantial influence on muscle output, a critical factor in the pathophysiology of sarcopenia[23]

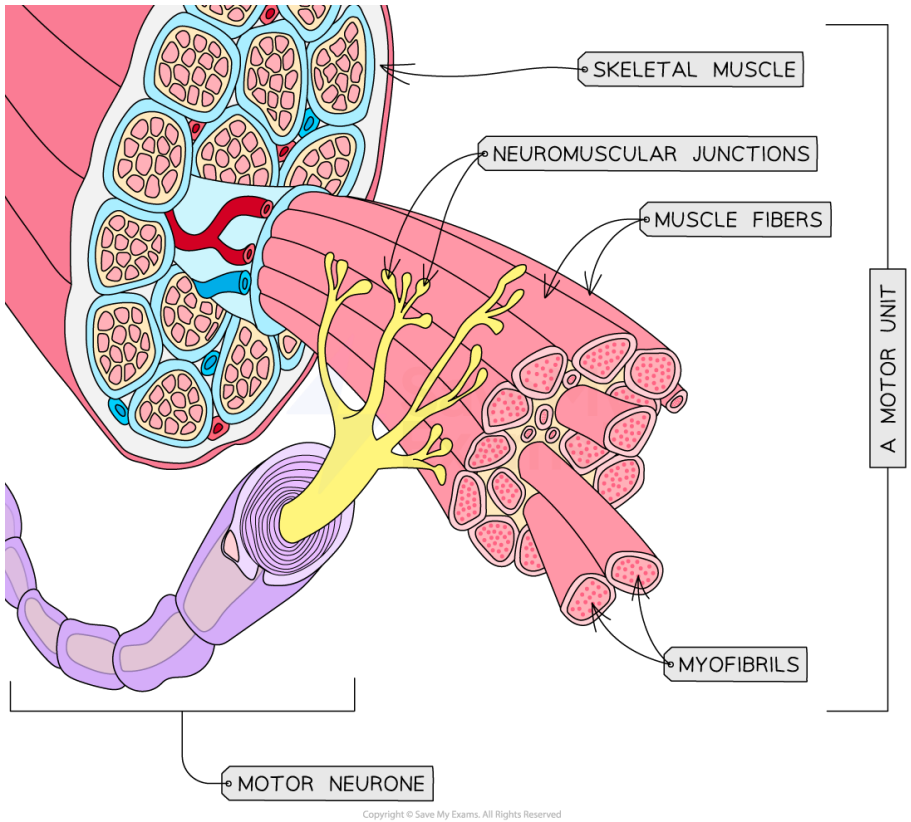

Figure 7 : the composition of motor unit [24]

II.2.1.3.2. Classification of Motor Units in Aging Muscle

The classification of motor units is based on a range of physiological, metabolic and molecular properties, which undergo alteration in cases of sarcopenia.

Physiologically Classification :

motor units in cat hindlimb muscles are categorized [23]as follows:

- slow-twitch, fatigue-resistant (S);
- fast-twitch, fatigue-resistant (FR);
- fast-twitch, fatigue-intermediate (FI);
- and fast-twitch, fatigable (FF)

Metabolic Classifications:

these cells are categorised as follows: [23]

- fast glycolytic (FG),
- fast oxidative glycolytic (FOG),

- slow oxidative (SO)

Moleculare Classification: motor units are defined by myosin heavy chain (MHC) profiles: The major histocompatibility complex (MHC) class I (slow) and fast isoforms, MHC IIa, IIx, and IIb, Typically, muscle fibres within a motor unit exhibit analogous biochemical and histochemical properties; however, in cases of sarcopenia, these properties undergo a shift, thereby contributing to functional decline[23].

These classifications provide a framework for understanding how motor unit remodelling affects muscle performance in the elderly.

II.2.1.3.3. Denervation and Reinnervation in Sarcopenia

A primary pathophysiological mechanism in sarcopenia is the repeated cycle of denervation and reinnervation, which remodels motor units and disrupts muscle innervation [25]. Denervation occurs when muscle fibers lose connection with their motor neuron, followed by reinnervation by the original axon or collateral sprouting from an adjacent motor neuron[5][25].. This process alters neuromuscular junction (NMJ) components, including reduced pre- and postsynaptic overlap, narrowed terminal axons, and changes in laminin and acetylcholine receptor distribution, often preceding myofiber atrophy [25].. These NMJ disruptions, observed in aged rodents and humans, initiate motor unit remodeling, contributing to sarcopenia's muscle wasting and weakness[25].

II.2.1.3.4. Motor Unit Loss and Muscle Atrophy

Motor neuron death and subsequent motor unit loss are central to sarcopenia's pathophysiology, significantly reducing muscle mass and function[25].. Electrophysiological studies estimate a motor unit reduction of up to 70% from the third to the ninth decade of life[25].. For example, McNeil et al. (2005) reported a 40% decrease in tibialis anterior motor units in older adults (65 years) compared to young adults (25 years), with an additional 33% loss in very old adults (~80 years). This accelerated loss after the seventh decade, driven by motor neuron death, exacerbates muscle atrophy and functional decline, hallmark features of sarcopenia[25].. Collateral reinnervation, where surviving motor neurons sprout to innervate denervated fibers, often shifts fast-twitch (Type II) fibers to slow-twitch (Type I), altering motor unit composition and impairing muscle performance[25].

II.2.1.3.5. Morphological Changes in Sarcopenic Muscle

Motor unit remodeling manifests in morphological changes that further the pathophysiology of sarcopenia. Denervation-reinnervation cycles lead to fiber type grouping, where muscle fibers of the same type cluster, and MHC co-expression, where single myofibers express multiple MHCs, reflecting disrupted innervation. [25]

Innervation regulates MHC expression, and its alteration in sarcopenia increases hybrid fibers, detectable through immunohistochemistry (IHC) with MHC antibodies [26]. Aging muscle also shows heterogeneous atrophy, angulated myofibers, and infiltration of fat cells, lipofuscin, and fibrous tissue, driven ding, enable precise quantification of these changes, confirming their role in sarcopenia's muscle deterioration[26]

II.2.1.3.6. Functional Consequences for Sarcopenia

The structural changes in motor units have profound functional implications for sarcopenia, impairing strength, contractile quality, and daily activities[25]. Motor unit loss and the shift to slower motor unit types reduce force output and contractile speed, diminishing work and power capacity [2]. Increased force variability, or loss of steadiness, results from fewer, larger motor units and variable firing rates, compromising smooth muscle control and contributing to balance deficits. This variability increases postural sway and reduces recovery from perturbations, elevating fall risk, a significant concern in sarcopenia[25]

.For instance, impaired rapid force generation can prevent recovery from a trip, leading to falls and loss of autonomy[25]

II.2.1.3.7. Neuromuscular Fatigue in Sarcopenia

Motor unit remodeling exacerbates neuromuscular fatigue, a key functional impairment in sarcopenia[25]. While healthy older adults may show similar or greater resistance to fatigue in isometric tasks compared to younger adults, very old adults (>75 years) exhibit increased fatigability, likely due to cumulative remodeling effects. Dynamic contractions consistently reveal greater fatigability in older adults, driven by reduced velocity and contractile strength. Motor unit firing rates decline after fatiguing tasks in both young and older adults, but recovery is delayed in older individuals, indicating reduced reserve for action potential transmission and worsening sarcopenia's functional limitations[25]

Motor unit remodeling is a cornerstone of sarcopenia's pathophysiology, driven by denervation-reinnervation cycles, motor unit loss, and altered fiber type composition. These changes result in morphological alterations, such as hybrid fibers and atrophy, and functional impairments, including reduced strength, increased fatigability, and heightened fall risk. By elucidating the neuromuscular mechanisms underlying sarcopenia, this section underscores the importance of motor unit remodeling in age-related muscle decline, paving the way for targeted therapeutic strategies.

II.2.2. Cellular and Molecular Mechanisms:

II.2.2.1. Protein Metabolism Imbalance:

II.2.2.1.1. Definition of MPS and MPB

Muscle protein synthesis (MPS) is the biological process by which new muscle proteins are generated, primarily from amino acids. It is essential for muscle growth, repair, and maintenance. Muscle protein breakdown (MPB), on the other hand, is the process through which muscle proteins are degraded into amino acids. In healthy muscle, these two processes are in balance, allowing for the maintenance of muscle mass. A net increase in MPS over MPB leads to muscle growth, while a net increase in MPB results in muscle loss.[27]

II.2.2.1.2. Muscle Protein Turnover

Skeletal muscle mass is maintained through a dynamic balance between muscle protein synthesis (MPS) and muscle protein breakdown (MPB). This balance is influenced by internal and external factors, including hormones, diet, physical activity, and age. The IGF-1/PI3K/Akt/mTOR pathway is central to this regulation, which responds to anabolic stimuli such as resistance exercise and essential amino acids.[28]

II.2.2.1.3. Key Anabolic Signaling Pathway

The mechanistic target of rapamycin (mTOR), especially in its mTORC1 complex, regulates translation initiation and ribosome production. Activation of mTOR by Akt promotes protein synthesis and muscle growth. In young adults, this pathway is robustly activated by exercise and dietary protein, particularly leucine-rich sources, resulting in hypertrophy.[28]

II.2.2.1.4. Anabolic Resistance with Aging

- **Blunted Muscle Response**

With aging, skeletal muscle becomes less responsive to anabolic signals—a phenomenon known as anabolic resistance. It is characterized by a reduced stimulation of MPS following protein intake or exercise. This leads to gradual muscle wasting and contributes significantly to sarcopenia. [28]

- **Mechanistic Insights**

The IGF-1/Akt/mTOR pathway becomes less efficient with age, with reduced and delayed phosphorylation of key proteins post-feeding or exercise. Additionally, insulin resistance, common in older adults and those with T2DM, limits nutrient and hormone delivery to muscle tissue, further impairing MPS[28]

- **Digestive and Transport Changes**

Aging also leads to increased splanchnic amino acid retention and reduced amino acid transport to muscles, weakening the anabolic response to protein intake.

II.2.2.1.5. Hormonal Contributions

- **Testosterone and Growth Hormone Decline**

Testosterone and growth hormone (GH), both vital for muscle anabolism, decline with age. Testosterone stimulates satellite cell activation and protein synthesis, while GH promotes amino acid uptake and IGF-1 production[29]

- **Estrogens and Myostatin**

In postmenopausal women, reduced estrogen levels contribute to muscle atrophy. Myostatin, a natural inhibitor of muscle growth, is often upregulated in aging muscle, further impeding protein synthesis. [29]

II.2.2.1.6. Amino Acids and Protein Intake

Importance of Amino Acids

Essential amino acids (EAAs), especially leucine, are critical for triggering MPS. Leucine directly activates mTORC1 and enhances muscle protein synthesis both in vitro and in vivo. Branched-chain amino acids (BCAAs) play a major role in regulating this process[29]

Protein Dose and Timing

Older adults require higher doses of high-quality protein (~30–40 g per meal) to maximize MPS. Fast-digesting proteins such as whey are particularly effective due to rapid absorption and high EAA content. Consuming protein soon after exercise amplifies MPS more effectively than at rest.

Digestion and Absorption

Age-related changes affect digestion and absorption. Fast-absorbing proteins like whey outperform slower ones like casein in promoting MPS in older adults. [29]

II.2.2.1.7. Nutritional and Exercise Interventions

Synergistic Effects of Exercise and Protein Resistance

training is a powerful anabolic stimulus. Its combination with protein intake can overcome some degree of anabolic resistance. While younger adults may respond well to lower protein doses, older adults often require higher quantities and frequent intake.

Type and Quality of Protein

Whey protein, rich in leucine, is more effective than casein or soy for older adults. Even some plant-based proteins, like mycoprotein, have shown promise when consumed in sufficient doses. [29]

II.2.2.2. Inflammation (Inflammaging):

II.2.2.2.1. Inflammaging and Systemic Inflammation

Inflammaging, a chronic low-grade inflammation associated with aging, is a key contributor to sarcopenia and related conditions like sarcopenic obesity[30]. It is driven by elevated levels of pro-inflammatory cytokines such as TNF-α, IL-6, IL-1, and chemokines, which promote inflammatory cell infiltration and muscle deterioration via the NF-κB pathway[30]. Inflammaging is exacerbated by lifestyle factors such as a sedentary lifestyle and high-fat diets, which increase the production of inflammatory molecules and contribute to insulin resistance and oxidative stress [30]. Diets high in saturated fats, like palmitic acid, activate the innate immune system, leading to inflammation and reduced muscle regeneration, while omega-3 polyunsaturated fatty acids (e.g., EPA, DHA) reduce inflammation and improve muscle function[30].

II.2.2.2.2. Direct Effects on Skeletal Muscle

Inflammation directly affects skeletal muscle by activating key signaling pathways, including NF-κB, JAK/STAT, and p38 MAPK, which disrupt the balance between protein synthesis and degradation [31]. The NF-κB pathway, activated by pro-inflammatory cytokines like TNF-α and IL-1, promotes the expression of ubiquitin-proteasome system (UPS)-related molecules, leading to proteolysis and muscle atrophy[31]. The JAK/STAT pathway, triggered by cytokines such as IL-6, enhances proteolysis through the upregulation of genes like MSTN, atrogin-1, and MuRF1, while inhibiting protein synthesis[31]. The p38 MAPK pathway, activated by stress signals, regulates inflammation and apoptosis, contributing to muscle atrophy by upregulating MuRF1 and atrogin-1[31]. These pathways collectively lead to muscle mass loss by promoting catabolic processes and inhibiting anabolic ones.

Pyroptosis and NLRP3 Inflammasome

The NLRP3 inflammasome, activated by inflammatory signals, triggers pyroptosis, a form of programmed cell death that contributes to sarcopenia by reducing myofiber size and glycolytic potential[30]. This process involves caspase-1 activation and gasdermin D cleavage, leading to membrane rupture and release of pro-inflammatory molecules like IL-1 and HMGB1[30]. Therapeutic interventions, such as BMP-7 and phlorotannin dieckol, have shown potential in attenuating pyroptosis and inflammation in muscle atrophy models[30].

II.2.2.2.3. Indirect Effects of Inflammation on Skeletal Muscle

Hypothalamic-Pituitary-Adrenal (HPA) Axis

Systemic inflammation indirectly contributes to muscle atrophy through the HPA axis, which regulates glucocorticoid synthesis and release[31]. Pro-inflammatory cytokines like IL-1 and IL-6 stimulate the HPA axis, increasing adrenocorticotropic hormone (ACTH) and glucocorticoid levels[31]. Glucocorticoids activate the glucocorticoid receptor (GR), which upregulates catabolic genes (e.g., atrogin-1, MuRF1) and inhibits mTOR, leading to muscle proteolysis and reduced protein synthesis[31] . Dysregulation of the HPA axis due to chronic inflammation can result in excessive glucocorticoid levels, exacerbating muscle atrophy[31]

Fat Metabolism and Cachexia

Inflammation influences fat metabolism, indirectly affecting skeletal muscle mass [31] Cytokines like TNF-α and IL-6 promote lipolysis and anorexia, reducing nutrient intake and

triggering muscle proteolysis to meet energy demands[31]. In cachexia models, IL-6 inhibits PPAR-α, impairing ketone production in the liver and increasing glucocorticoid release via the HPA axis, which enhances muscle degradation [31]. Treatments like fenofibrate, a PPAR-α agonist, can restore ketone production, reducing the need for muscle-derived amino acids[31]

II.2.2.2.4. Key Inflammatory Mediators in Muscle Repair and Atrophy

II.2.2.2.4.1. Pro-Inflammatory Cytokines

- **TNF-α**: Activates NF-κB, JNK, and AP-1 pathways, promoting proteolysis and inhibiting myogenesis by silencing Notch1 and reducing Pax7 expression. Chronic TNF-α levels are linked to muscle wasting in conditions [32].
- **IL-6**: Exhibits both pro- and anti-inflammatory effects, depending on the context[32]. It activates JAK/STAT3, promoting proteolysis and inhibiting IGF-1, but also supports muscle hypertrophy during exercise. Chronic IL-6 elevation is associated with muscle wasting[32]
- **IL-1β**: Stimulates inflammatory responses and activates NF-κB, contributing to muscle damage .[33]
- **IFN-γ**: Signals through JAK/STAT1, promoting myoblast proliferation but inhibiting differentiation at high doses by inducing CIITA, which silences muscle-specific genes [3]. It supports muscle repair at low doses but is anti-myogenic chronically[32]
- **IL-17**: Enhances pro-inflammatory cytokine production, contributing to chronic inflammation and muscle damage in conditions like Duchenne muscular dystrophy[32]

II.2.2.2.4.2. Anti-Inflammatory Cytokines

- **IL-4**: Promotes myoblast fusion and M2 macrophage activation, supporting muscle regeneration[32]. It regulates adhesion molecules like ICAM1 and VCAM-1, aiding myotube formation[32]
- **IL-10**: Inhibits pro-inflammatory cytokines (e.g., TNF-α, IL-6) and converts M1 macrophages to the regenerative M2c phenotype, protecting against muscle atrophy [32]It rescues myogenin expression and prevents JNK phosphorylation[32]

II.2.2.2.4.3. TGF-β Family

- **TGF-β**: Inhibits myogenesis by blocking MyoD and myogenin activity via Smad3, promoting fibrosis in muscle repair[32]. It is upregulated post-injury, contributing to inflammatory responses[32]
- **Myostatin**: Negatively regulates muscle mass, activating Smad2/3 and inhibiting muscle growth [32]. Its inhibition enhances muscle regeneration [32]
- **GDF15**: Exhibits anti-inflammatory properties but is elevated in chronic inflammatory diseases, potentially regulating IL-6 and TGF-β responses[32]

II.2.2.2.4.4. TWEAK

TWEAK, a TNF superfamily member, activates NF-κB and MAPK pathways, promoting proteolysis via MuRF1 and MAFbx upregulation [32]. It contributes to fibrosis and inflammation in chronic disorders, cooperating with cytokines like TNF-α and IL-17[32]

II.2.2.2.5. Inflammatory Response Pathways in Muscle Regeneration

The inflammatory response to skeletal muscle injury is a coordinated process involving innate and adaptive immune cells. Pro-inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α) and microbial agents trigger pathways like JAK/STAT, MAPK, and NF-κB, initiating inflammation Neutrophils and M1 macrophages respond early, promoting inflammation, followed by M2 macrophages, which resolve inflammation and support regeneration. CD8+ T cells and T regulatory cells contribute later, aiding tissue repair. Regeneration involves myogenesis and new muscle formation, distinct from hypertrophy or adaptation. Phagocytosis by immune cells is critical for clearing debris and enabling regeneration[33]

II.2.2.3. Oxidative Stress:

Oxidative stress, an imbalance between reactive oxygen species (ROS) and antioxidants, is a key driver of sarcopenia, exacerbating muscle loss by disrupting protein homeostasis. Aging increases ROS production, primarily from mitochondria and NADPH oxidase, damaging DNA, proteins, and lipids, and impairing muscle function. Low antioxidant levels, such as carotenoids, correlate with reduced muscle strength and mobility[34]

II.2.2.3.1. Sources and Mechanisms

ROS, including superoxide, hydrogen peroxide, and hydroxyl radicals, are generated endogenously (e.g., mitochondrial respiratory chain, NADPH oxidase) and exogenously (e.g., pollution, drugs). These species oxidize cellular components, forming markers like protein carbonyls, nitrotyrosine, and 8-oxoGuo. Mitochondria, major ROS producers, are also primary targets, leading to dysfunction critical in sarcopenia [. Aging reduces antioxidant defenses (e.g., SOD, catalase, glutathione peroxidase), worsening oxidative damage[35]

II.2.2.3.2. Impact on Muscle Function

Protein and Cellular Damage

Oxidative stress disrupts the balance of muscle protein synthesis and degradation, blunting anabolic signaling (e.g., Akt/mTOR) and increasing catabolism. ROS-induced damage to myogenic proteins and autophagy impairs satellite cell differentiation and muscle regeneration. In sarcoplasmic reticulum, ROS alter excitation-contraction coupling by oxidizing Ryanodine receptors (RyR1), reducing calcium release and muscle contraction efficiency[36].

Mitochondrial Dysfunction

Mitochondrial dysfunction, driven by ROS, is central to sarcopenia. Aging alters mitochondrial dynamics (fusion/fission) and mitophagy, accumulating dysfunctional mitochondria. Reduced Parkin-PINK1 activity and voltage-dependent anion channel recruitment impair mitophagy, exacerbating muscle loss. ROS also trigger apoptosis via caspase and JNK pathways, contributing to muscle atrophy[37]

II.2.2.3.3. Oxidative Stress and Inflammation

Inflammaging

Oxidative stress induces inflammaging, a chronic inflammatory state, by activating NF-κB and increasing pro-inflammatory cytokines (e.g., TNF-α, IL-6). These cytokines promote muscle catabolism, inhibit protein synthesis, and impair muscle integrity. Anti-inflammatory cytokines (e.g., IL-4, IL-10) counteract these effects, supporting muscle regeneration[37]

Feedback Loop

ROS activate macrophages and neutrophils, releasing more ROS and cytokines, forming a vicious cycle with oxidative stress and inflammation. This cycle reduces

antioxidant capacity, inhibits satellite cell activation, and diminishes muscle regeneration, worsening sarcopenia[38]

II.2.2.4. Hormonal Changes:

GH and IGF-I

Somatopause reduces GH/IGF-I, linked to muscle loss, but GH therapy increases mass without strength gains and risks insulin resistance. Local IGF-I promotes muscle hypertrophy and regeneration, counteracting sarcopenia[39]

Adrenal Hormones

Increased cortisol promotes proteolysis and reduces muscle mass; DHEA declines, with unclear effects on muscle[40]

Gonadal Steroids

Testosterone decline reduces muscle mass; TRT improves mass but not always strength Estrogen loss in menopause accelerates muscle loss; HRT may enhance strength but carries risks[40]

Adipokines

Leptin supports myogenesis but is reduced in sarcopenia; resistance in obesity worsens loss High adiponectin levels may reflect muscle loss; resistin inhibits myogenesis. [40]

Angiotensin II

Elevated levels induce proteolysis; ACE1 inhibitors increase muscle mass and IGF-I [40]

Vitamin D

Deficiency correlates with muscle loss; supplementation aids strength with exercise[40]

Thyroid Hormones

Declining TH reduces myogenesis; low FT3 and altered TSH levels link to sarcopenia[40]

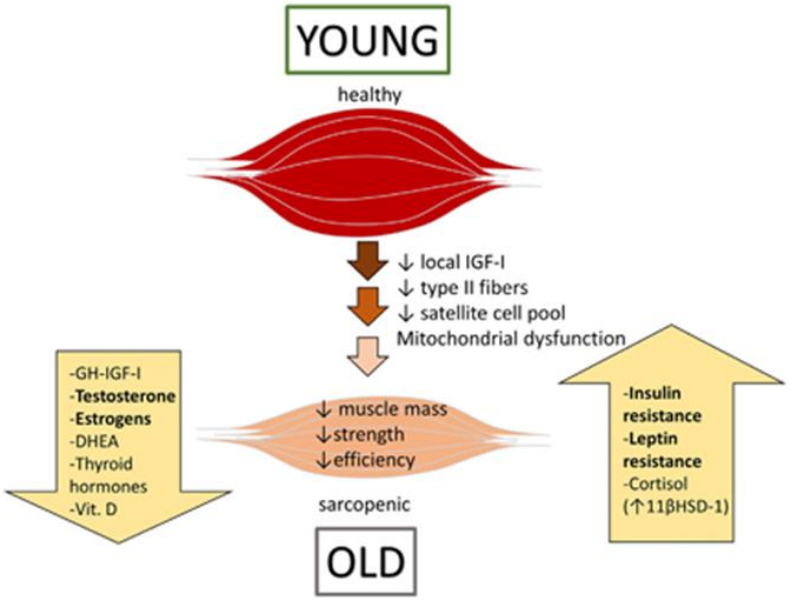

Figure 8 : main age-related hormonal alterations involved in the development of sarcopenia[40]

II.2.2.5. Mitochondrial Dysfunction:

II.2.2.5.1. Mitochondrial Homeostasis in Skeletal Muscle

Mitochondria, critical for skeletal muscle bioenergetics, decline with age, reducing aerobic capacity. Subsarcolemmal (SS) and intermyofibrillar (IMF) mitochondria differ in function and adaptation; SS handle gene expression and ROS resistance, while IMF support oxidative phosphorylation and Ca^{2+} flux. Mitochondrial dynamics (fusion/fission) and turnover (biogenesis/mitophagy) maintain energy balance, regulated by proteins like Mfn1/2, OPA1, Drp1, and PGC-1α. Exercise enhances fusion and biogenesis via AMPK and SIRT1, countering dysfunction[41]

II.2.2.5.2. Age-Related Mitochondrial Impairments

Mitochondrial dysfunction drives sarcopenia through reduced ATP production, increased ROS/RNS, and apoptosis activation. Aging lowers mitochondrial mass, enzyme activity, and oxidative phosphorylation, with mtDNA mutations and deletions exacerbating damage. Impaired dynamics favor fission, and reduced PGC-1α expression limits biogenesis. Mitophagy dysregulation and lysosomal dysfunction lead to accumulation of damaged mitochondria. Physical activity mitigates these effects, preserving mitochondrial function[42]

II.2.2.5.3. Mitochondria and Aging

Mitochondrial dysfunction, a hallmark of aging, results from mtDNA mutations, causing defective electron transport chain function, ROS overproduction, and bioenergetic failure. Antioxidant defenses upregulate but fail to counter oxidative damage in advanced age. Lower mtDNA copy numbers and higher deletions correlate with frailty, while centenarians with less frailty show higher mtDNA copies[43]

II.2.2.5.4. Mitochondrial Role in Sarcopenia

Mitochondria drive sarcopenia via mtDNA damage, impairing ATP synthesis and increasing ROS, which triggers apoptosis and muscle loss. Reduced PGC-1α activity disrupts biogenesis and mitophagy, worsening dysfunction. Exercise-induced AMPK/SIRT1/PGC-1α activation promotes biogenesis and mitohormesis, enhancing mitochondrial function and preventing sarcopenia[44]

II.2.2.5.5. Cellular Senescence and Inflammation

Mitochondrial dysfunction induces cellular senescence through ROS-mediated DNA damage and telomere shortening, impairing muscle regeneration. Senescent cells contribute to inflammaging, releasing pro-inflammatory cytokines (e.g., IL-6) that disrupt satellite cell function and promote muscle catabolism[45]

II.2.2.5.6. Mitochondrial Autophagy (Mitophagy)

Mitophagy, a selective autophagy process, removes damaged mitochondria, regulated by AMPK, PINK1/PARKIN, and FoxO3. Aging impairs mitophagy, leading to dysfunctional mitochondrial accumulation, exacerbated by lysosomal dysfunction and lipofuscin buildup. Excessive or insufficient autophagy can cause muscle atrophy; PGC-1α overexpression mitigates this by enhancing biogenesis and turnover. Exercise and calorie restriction preserve autophagy, reducing oxidative stress and supporting muscle homeostasis[45]

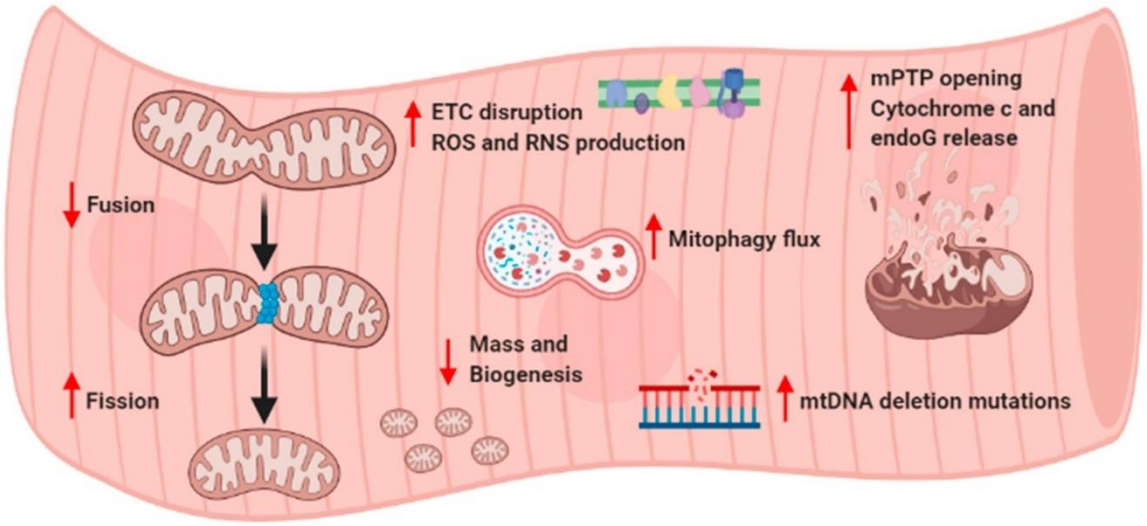

Figure 9 : General summary of altered skeletal muscle mitochondrial pathways in sarcopenia.[43]

II.2.2.6. Satellite Cell Dysfunction

Satellite cells are adult muscle stem cells located between the sarcolemma and the basal lamina of muscle fibers. In healthy skeletal muscle, these cells remain quiescent but become activated in response to stress or injury. They are crucial for maintaining muscle homeostasis, enabling growth, regeneration, and repair throughout life[46]

II.2.2.6.1. Activation and Regenerative Role

In the event of damage to muscle tissue, satellite cells are activated, proliferate, and differentiate into myogenic precursor cells that subsequently fuse with existing fibres or form new ones. Furthermore, a proportion of daughter cells undergo self-renewal, thereby replenishing the satellite cell pool. This regeneration process is imperative for preserving muscle mass and function, particularly in cases of trauma or metabolic stress[47]

II.2.2.6.2. Satellite Cell Dysfunction Mechanisms in Sarcopenia

1. **Impaired Activation Capacity**

With aging, satellite cells exhibit reduced responsiveness to key mitogenic factors such as hepatocyte growth factor (HGF) and insulin-like growth factor 1 (IGF-1). This decline in sensitivity results in diminished activation, delayed regeneration, and inadequate repair following muscle damage[48]

2. **Defects in Asymmetric Division**

Healthy satellite cells divide asymmetrically to generate both committed myogenic cells and self-renewing stem-like cells. In sarcopenia, disruptions in polarity and signaling pathways impair this balance, leading to excessive commitment and loss of the stem cell pool. This reduces the long-term regenerative capacity of muscle[48]

3. Loss of Stem-Like Subpopulations

The rare $Pax7^{+}/Myf5^{-}$ satellite cell subpopulation has been identified as essential for self-renewal and niche repopulation. Aging preferentially depletes this subset, weakening the muscle's ability to recover from injury and contributing to progressive atrophy[48]

4. Niche Alterations

The satellite cell microenvironment (or niche) becomes increasingly dysfunctional with age. Changes such as reduced capillary density, fibrotic remodeling, altered ECM composition, and a pro-inflammatory milieu disrupt the signaling cues necessary for maintaining quiescence and supporting regeneration[48]

5. Shift in Cell Fate

Under pathological conditions, satellite cells can adopt non-myogenic fates, differentiating into adipocytes or fibroblasts instead of myoblasts. This shift leads to fat infiltration and fibrosis in skeletal muscle, reducing its functional quality and contributing to sarcopenia[48]

II.2.2.6.3. Functional Consequences

Satellite cell dysfunction directly contributes to reduced muscle regenerative capacity, impaired adaptation to exercise, and delayed recovery from injury. Over time, this leads to progressive muscle fiber atrophy, decreased strength, and higher vulnerability to metabolic stress, all of which are characteristic features of sarcopenia[49]

II.2.2.7. Neural Factors:

Sarcopenia, the age-related decline in muscle mass, strength, and function, is profoundly influenced by neural mechanisms that impair the connection between motor neurons and muscle fibers. These neural factors, encompassing neuromuscular junction (NMJ) instability, sympathetic nervous system (SNS) dysregulation, and motor neuron deterioration, drive muscle atrophy, weakness, and increased fall risk, central to sarcopenia's pathophysiology.

II.2.2.7.1. Neuromuscular Junction and Sarcopenia

The neuromuscular junction (NMJ) is the critical synapse where motor neurons activate muscle fibers, which are essential for muscle contraction [50]. The following components are of paramount importance:

- Presynaptic terminal axons release acetylcholine (ACh) [50]
- Perisynaptic Schwann cells (PSCs) have been identified as a key component in the process of axonal sprouting[26]
- The presence of post-synaptic ACh receptor (AChR) clusters on the muscle fiber has been documented[26]

It has been established that neural agrin, a pivotal signalling molecule, activates muscle-specific kinase (MuSK) via low-density lipoprotein receptor-related protein 4 (LRP4), thereby ensuring AChR clustering[26]

In aging, increased agrin cleavage and reduced MuSK levels impair this signaling, resembling premature aging seen in MuSK-related myasthenia gravis[26]

II.2.2.7.2. Age-Related NMJ Instability

Aging induces structural and functional NMJ changes that exacerbate sarcopenia [50], [51] Fragmented NMJs, reduced presynaptic vesicles, and degenerated junctional folds impair neuromuscular transmission, reducing the safety factor—the surplus ACh release ensuring reliable muscle activation[50]

Key Structural Changes:

- Fragmented AChR clusters and fewer synaptic vesicles in rodents[51]
- Irregular presynaptic terminals and increased postsynaptic membrane length in humans[51]
- Selective loss of active zone proteins (P/Q-type VGCC, Bassoon), reducing synaptic vesicle release[51]

II.2.2.7.3. Denervation and Muscle Atrophy

NMJ instability leads to denervation, a primary driver of muscle atrophy in sarcopenia [51]. Denervated fibers, marked by sodium channel isoform Nav1.5 and neural cell adhesion molecule (NCAM), exhibit significant size reduction and upregulated atrogenes like

MAFbx, MuRF1, MuSA1, and SMART, targeting proteins for proteasomal degradation [1, 2]. The autophagy-lysosome pathway, activated by mitochondrial reactive oxygen species, further degrades cellular components [51]

II.2.2.7.4. Sympathetic Nervous System Dysregulation

The sympathetic nervous system (SNS) regulates NMJ stability and muscle innervation, and its age-related decline contributes to sarcopenia Sympathetic axons innervate NMJs, influencing AChR stability via noradrenaline (NA) and Gαi2 signaling. [51]

SNS Impacts in Sarcopenia:

- Sympathectomy reduces NA by 80%, increasing MuRF1 and Hdac4, leading to atrophy[51]
- Reduced Gαi2 levels promote denervation, reversible by restoring Gαi2 signaling[51]
- Extensive sympathetic innervation in hindlimb muscles supports NMJ function[51]

II.2.2.7.5. Functional Impairments in Sarcopenia

Neural alterations significantly impair neuromuscular performance, worsening sarcopenia's impact on daily life. [50], [51] Reduced NMJ transmission efficiency, marked by increas ed jitter and synaptic blockade in rodents, limits muscle activation [51]. In humans, mild increases in jitter suggest altered neurotransmission, contributing to weakness [51]. Slower motor neuron firing rates and motor unit loss increase fatigability, particularly in dynamic tasks, and heighten fall risk, limiting activities like walking or stair climbing[52]

II.2.2.7.6. Interventions Targeting Neural Factors

The NMJ's plasticity offers potential for interventions to mitigate sarcopenia [26]. Exercise and calorie restriction attenuate NMJ distortion in aging mice and humans, while increased expression of plasticity markers like agrin and growth-associated protein 43 suggests ongoing remodeling. SNS-targeted interventions, such as restoring Gαi2 signaling, prevent denervation and atrophy, highlighting the therapeutic potential of neural modulation. These strategies emphasize the importance of addressing neural deficits to improve muscle function in sarcopenia. [26].

II.3. Risk Factors for Sarcopenia

II.3.1. Non-Modifiable Risk Factors:

II.3.1.1. Age:

Age-Related Prevalence and Screening

Age significantly influences sarcopenia risk, with prevalence rising sharply in older adults, particularly those over 75 years, due to accelerated muscle mass and strength decline.[53] Daycare centers, catering to frail elderly, show higher sarcopenia prevalence than community settings, underscoring the need for regular screening using accessible tools like the AWGS 2019 guidelines to enable early intervention and prevent progression[54].

Impact on Muscle Function

Aging reduces force-generating capacity due to muscle mass loss (up to 30% by age 80), particularly in lower limb type II fibers, alongside changes in muscle architecture, increased connective tissue, fat infiltration, and impaired neural control. These alterations compromise balance, increase fall risk, and contribute to disability, osteopenia, and fractures[55]

II.3.1.2. Sex:

Sex influences sarcopenia risk, with inconsistent findings across studies; some report higher prevalence in females due to faster hormonal declines, particularly estrogens, post-65, while others indicate higher prevalence in males, especially with chronic kidney disease (CKD)[56]. Males may face significantly elevated risks of possible, confirmed, and severe sarcopenia, particularly in predialysis CKD, necessitating targeted prevention in this group.[57]

Hormonal and Metabolic Mechanisms

In females, reduced insulin-like growth factor-1 (IGF-1) levels correlate with sarcopenia, reflecting anabolic decline, while in males, elevated myostatin levels inhibit muscle growth, driving catabolic processes. Hormonal changes, such as estrogen reduction in women, accelerate muscle loss post-menopause, whereas testosterone's anabolic effects in men may mitigate prevalence differences, though not uniformly across populations[58]

II.3.1.3. Genetics:

Genetic Influence on Muscle Traits

Genetic factors significantly contribute to sarcopenia risk by influencing skeletal muscle mass, strength, and fiber type proportion, with heritability estimates of 85–90% for muscle mass and 77–90% for strength in twins, though only 45% of muscle fiber type variance is genetically determined. Over 200 autosomal and 18 mitochondrial genes are linked to fitness and performance, indicating sarcopenia as a polygenic trait with high interindividual variability in resistance training responses (e.g., muscle cross-sectional area changes from −2.5% to 59%). Transmissible variance accounts for 63% of muscular strength, with genetic factors contributing 30% and cultural inheritance 31%, highlighting both hereditary and environmental roles[55]

Polygenic Risk Scores for Sarcopenia

Single gene polymorphisms, such as those in ACTN3, VDR, and CVI, each contribute modestly (<5%) to sarcopenia risk, but a genetic risk score combining multiple single nucleotide polymorphisms (SNPs) like MTHFR C, ACTN3 X, and NRF2 C explains up to 39% of interindividual variability. Individuals with three or more unfavorable alleles face a 1.06-fold higher sarcopenia likelihood, with a risk score cut-off of ≥58.3% effectively classifying those at elevated risk, supporting the potential of polygenic risk scores for predicting sarcopenia susceptibility[59]

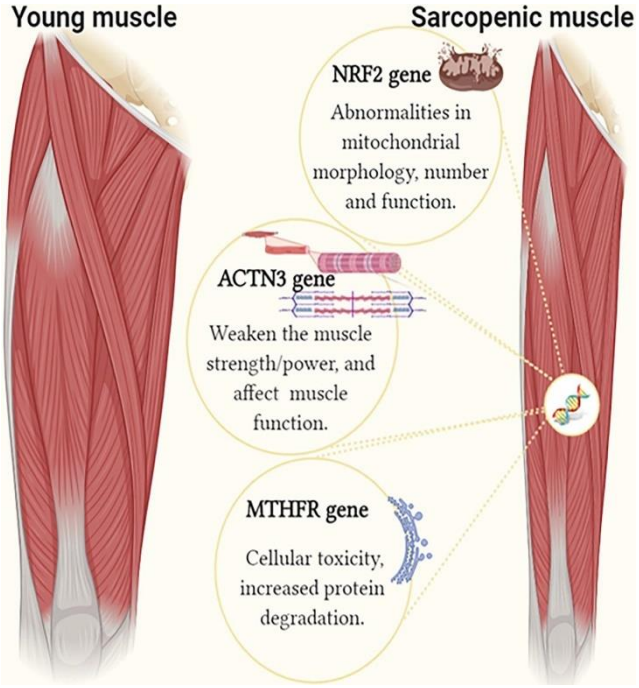

Figure 10 : *the identified genetic factors in individuals with sarcopenia compared to controls[59]*

II.3.2. Modifiable Risk Factors

II.3.2.1. Physical Inactivity:

Association with Sarcopenia Risk

Physical inactivity significantly increases sarcopenia risk, with self-reported low physical activity (PA) levels linked to higher sarcopenia prevalence in community-dwelling older adults not meeting PA guidelines and those with recent hip fractures (HF). Probable sarcopenia, indicated by low handgrip strength, is particularly prevalent post-HF, exacerbated by immobilization and inflammatory responses, highlighting the acute sarcopenia risk in this group. In contrast, accelerometer-measured PA shows no clear association with sarcopenia, possibly due to measurement limitations or behavioral changes during monitoring[60]

Mechanisms and Implications

Sedentary behavior displaces moderate-to-vigorous physical activity (MVPA), promoting chronic low-grade inflammation, which accelerates muscle loss and sarcopenia. MVPA, unlike light PA, provides sufficient stimuli to maintain muscle strength, reducing sarcopenia risk, as evidenced by studies showing up to a 2-fold increased risk with low PA. Post-HF, low PA, often characterized by resting or sitting, impairs functional recovery, prolongs sedentary behavior, and worsens muscle wasting due to myosteatosis and reduced amino acid reserves[60]

II.3.2.2. Nutritional Deficiencies:

Impact of Declining Food Intake

Nutritional deficiencies, driven by a 25% reduction in food intake between ages 40 and 70, exacerbate sarcopenia risk in older adults due to the "anorexia of ageing," influenced by physiological (e.g., reduced appetite, taste loss), psychological (e.g., depression), and social (e.g., eating alone) factors. Low energy intake leads to muscle mass loss if not balanced with reduced expenditure, while inadequate nutrient intake, particularly of protein, vitaminD, antioxidants, and long-chain polyunsaturated fatty acids (LCPUFAs), impairs muscle synthesis and function, creating a vicious cycle with declining physical capability[61]

Key Nutrients and Muscle Health

Protein is considered a key nutrient. Dietary protein provides amino acids that are needed for the synthesis of muscle protein, and importantly, absorbed amino acids have a stimulatory effect on muscle protein synthesis after feeding. Vitamin D, via its receptor in skeletal muscle, supports strength, with low status linked to frailty, but supplementation benefits are inconsistent. Antioxidants (e.g., carotenoids, selenium, vitamins C and E) counter oxidative stress, with higher status predicting better physical function, while n-3 LCPUFAs reduce inflammation, potentially enhancing muscle protein synthesis. Inadequate intakes of these nutrients, common in older adults, heighten sarcopenia risk[61]

II.3.2.3. Chronic Diseases and Sarcopenia

Chronic diseases, including heart disease, chronic obstructive pulmonary disease (COPD), liver disease, and stroke, significantly accelerate sarcopenia by promoting muscle catabolism through chronic inflammation, metabolic disorders, and reduced physical activity. Liver disease exacerbates muscle loss via malnutrition, impaired protein synthesis, and systemic inflammation, while chronic heart failure and COPD increase sarcopenia risk due to heightened catabolic states Sarcopenia and chronic diseases exhibit a bidirectional relationship, where sarcopenia worsens disease progression, increases mortality, and reduces quality of life, particularly in cardiovascular and liver conditions.[62]

II.3.2.4. Lifestyle Factors Influencing Sarcopenia

Lifestyle factors critically influence sarcopenia risk, with sedentary behavior and excessive high-intensity exercise both contributing to muscle loss, whereas moderate activities like brisk walking or strength training help maintain muscle mass. Poor sleep quality, whether insufficient or excessive, disrupts endocrine and inflammatory responses, accelerating muscle decline. Social isolation, linked to reduced physical activity and mental health issues like depression, significantly elevates sarcopenia risk, emphasizing the protective role of social engagement.[62]

II.4. Clinical Manifestations and Consequences of Sarcopenia

II.4.1. Physical Signs and Symptoms:

The symptoms of sarcopenia often become apparent when they begin to hinder everyday activities. Elderly individuals, through self-reporting in the SARC-F questionnaire, have noted several difficulties. These include [63]

- trouble climbing stairs

- experiencing gait difficulties (problems with walking)
- a history of falls
- challenges in lifting or carrying loads (reduced strength for carrying objects)
- difficulty getting up from a chair (decreased strength for rising)

Beyond these self-reported limitations, sarcopenia also manifests as a noticeable decrease in muscle size, general weakness, reduced endurance, and poor balance. [64]

Furthermore, individuals with sarcopenia may exhibit slow walking speed and visibly shrinking muscles. These signs collectively indicate the progressive loss of muscle tissue and its functional capacity. [65]

II.4.2. Functional Limitations and Disability:

1. Impaired ability to perform activities of daily living (ADLs):

The term "Activities of Daily Living (ADLs)" collectively describes fundamental self-care skills essential for independent living, such as eating, bathing, and mobility. ADL proficiency serves as a crucial indicator of an individual's functional status. The inability to perform these basic ADLs often results in dependence on others or mechanical devices, potentially leading to unsafe conditions and a diminished quality of life.[66]

Basic ADLs encompass the following key categories:

Ambulating: The capacity to move between positions and walk independently.

Feeding: The ability to feed oneself.

Dressing: The ability to select and put on appropriate clothing.

Personal hygiene: The ability to bathe, groom, and maintain dental, nail, and hair care.

Continence: The ability to control bladder and bowel function.

Toileting: The ability to get to and from the toilet, use it appropriately, and clean oneself.[66]

Previous research has consistently demonstrated a significant association between sarcopenia and difficulties with ADLs in older adults living in the community. Sarcopenia contributes to decreased energy expenditure due to a reduction in basal metabolic rate resulting from the loss of skeletal muscle mass. This, in turn, can lead to a decrease in appetite, potentially further accelerating the progression of sarcopenia.[67]

Furthermore, the muscle weakness and decline in physical function directly associated with sarcopenia significantly contribute to the impairment of ADL performance. This impairment often leads to reduced activity levels, creating a detrimental cycle where decreased activity further exacerbates muscle loss and weakness, thus perpetuating functional decline.[67]

2. Increased risk of falls and fractures.

Falls are a significant contributor to disability, particularly among older adults. A fall is an unintentional event in which a person comes to rest on the ground or a lower level, not caused by a major intrinsic event or overwhelming hazard. Falls are directly linked to increased mortality, morbidity, and reduced functionality, and they frequently occur in older adults.[68]

An important underlying cause of falls in older adults is sarcopenia. Sarcopenia, which can be associated with nutritional decline, prolonged hospitalization, and/or chronic illness, leads to a decrease in muscle mass, volume, and coordination. This is often accompanied by phenotypic changes, such as the selective loss of white muscle fibers, which ultimately increases the propensity for falls and, consequently, the susceptibility to injuries like fractures.[68]

II.4.3. Impact on Metabolic Health:

Sarcopenia, characterized by the decline in muscle mass, quality, and function, intricately intertwines with various facets of metabolic health, often culminating in significant health adversities.

1. Impaired glucose metabolism and insulin resistance:

The skeletal muscle, a principal site for insulin-mediated glucose metabolism, faces compromised functionality with sarcopenia. This deterioration is closely associated with the onset of insulin resistance, a key precursor to type 2 diabetes mellitus, thereby underscoring the condition's critical relevance in glycemic control.[69]

2. Increased risk of metabolic syndrome:

The nexus between metabolic syndrome and sarcopenia has garnered increasing attention in recent years.

Metabolic syndrome is an accumulation of several disorders that raise the risk of atherosclerotic cardiovascular disease, including myocardial infarction, cerebrovascular

accidents, peripheral vascular diseases, insulin resistance, and type II diabetes mellitus.[70] This coexistence not only diminishes the individual's quality of life but also escalates the propensity for frailty, physical dependency, and heightened morbidity and mortality risks.[69]

Altered lipid profiles:

Metabolic syndrome, frequently accompanying sarcopenia, is marked by an array of metabolic disturbances, including dyslipidemia. The excessive accumulation of visceral fat, coupled with abnormalities in blood pressure, fasting glucose, and lipid levels, collectively elevates the risk spectrum for type 2 diabetes mellitus, cardiovascular diseases, and certain malignancies.[69]

Furthermore, it's worth noting that conditions like starvation, which induce a combined loss of fat and muscle mass, underscore the delicate balance of tissue maintenance, contrasting with the more chronic muscle wasting observed in sarcopenia

II.4.4. Increased Morbidity and Mortality

Sarcopenia, far from being a mere byproduct of aging, emerges as a critical health issue with profound implications for older adults. It's associated with a cascade of adverse outcomes that significantly diminish quality of life and increase the risk of serious health events.

1. **Increased risk of hospitalization and institutionalization:**

The research reveals a troubling link between sarcopenia and the increased likelihood of hospitalization.[71] This suggests that individuals with sarcopenia are more vulnerable to health crises that require medical intervention. Furthermore, there's evidence pointing to a greater need for long-term care in institutions for those affected by sarcopenia. This highlights the debilitating impact of muscle loss on independent living.[72]

It's important to note that the very experience of hospitalization can itself exacerbate sarcopenia. The combination of acute inflammation and reduced physical activity during hospital stays can lead to a rapid decline in muscle mass and function, pushing some individuals into a state of acute sarcopenia. This creates a cruel cycle where the treatment for one health issue contributes to the development of another.[72]

2. **Elevated overall mortality risk:**

The most alarming consequence of sarcopenia is its strong association with an increased risk of death.

Multiple studies and meta-analyses have consistently demonstrated that individuals with sarcopenia face a significantly higher mortality risk compared to their non-sarcopenic peers. In one meta-analysis, the risk of death was found to be four times higher in sarcopenic patients[73].

This increased risk transcends specific settings, affecting community-dwelling individuals, hospitalized patients, and those in nursing homes.[73]

Moreover, the risk of mortality appears to escalate with age, posing a particularly grave threat to those over 79 years old [72]

Recent research has further emphasized this connection, with studies showing that older patients admitted to acute geriatric wards have a higher prevalence of sarcopenia. Sarcopenia, when diagnosed using specific criteria (EWGSOP and FNIH), was associated with a substantially higher probability of mortality (up to 4.3 times greater) in these patients.[73]

sarcopenia presents a complex and serious challenge, significantly impacting the health and longevity of older adults. The evidence strongly underscores the need for increased awareness, early detection, and effective interventions to mitigate its devastating consequences.

II.4.5. Quality of Life Implications:

Sarcopenia, has significant implications for the quality of life (QoL) among older adults.

1. Reduced Self-Esteem and Body Image

Sarcopenia profoundly affects physical health-related QoL, with older adults experiencing nearly three times the likelihood of poor QoL in this domain[74]. The decline in muscle mass and function often manifests as mobility impairments, bodily pain, and loss of independence, which can erode self-esteem and negatively alter body image. These physical limitations hinder the performance of daily activities, contributing to a diminished sense of self-worth. Studies indicate that even early-stage sarcopenia can have a deleterious impact on physical health-related QoL, underscoring the pervasive influence of muscle loss on self-perception[74]

2. **Social Isolation and Depression**

Sarcopenia significantly impacts psychological QoL, increasing the likelihood of poor psychological well-being by 2.7 times [74]. It is associated with depression, driven by shared factors like physical inactivity and inflammation, with a 24% higher sarcopenia risk in depressed individuals [74].. Reduced physical function limits social engagement, exacerbating isolation, particularly in those aged 60–70 years[75].

II.5. Diagnosis and Assessment of Sarcopenia

II.5.1. Screening Tools for Sarcopenia

The implementation of effective screening procedures for sarcopenia is of paramount importance for the purpose of facilitating early identification and intervention, a necessity that is particularly pronounced in older adults, given the association between this condition and functional decline as well as diminished quality of life.

The SARC-F questionnaire has emerged as a widely recommended and validated tool for sarcopenia screening, supported by major consensus groups and adapted for diverse clinical and community settings.

Brief Questionnaires (e.g., SARC-F)

The SARC-F questionnaire is a simple, five-item screening tool designed to identify individuals at risk of sarcopenia by assessing strength, assistance with walking, rising from a chair, climbing stairs, and falls[76], [77], [78]. Each item is scored from 0 to 2, with a total score of ≥4 indicating a risk of sarcopenia [77], [78]. This cutoff is associated with lower quality of life and higher mortality risk, making it a valuable indicator for clinical intervention [77].

Table 1 : SARC-F Score [76]

Component	Question	Scoring
Strength	How much difficulty do you have in lifting and carrying 10 pound?	None = 0 Some = 1 A lot or unable = 2
Assistance in walking	How much difficulty do you have walking across a room?	None = 0 Some= 1 A lot, use aids, or unable = 2
Rise from a chair	How much difficulty do you have transferring from a chair or bed?	None = 0 Some= 1 A lot or unable without help = 2
Climb stairs	How much difficulty do you have climbing a flight of 10 stairs?	None = 0 Some= 1 A lot or unable = 2
Falls	How many times have you fallen in the past year?	None = 0 1-3 falls = 1 ≥ 4 falls = 2

The European Working Group on Sarcopenia in Older People (EWGSOP2) and the Asian Working Group for Sarcopenia (AWGS2) endorse SARC-F as a primary screening tool due to its ease of use and international applicability[76], [78]. Translated versions of SARC-F have been validated across multiple languages, enhancing its utility in diverse populations [77]

II.5.2. Measurement of Muscle Mass:

1. **Dual-energy X-ray Absorptiometry (DXA):**

Accurate measurement of muscle mass is imperative for the diagnosis of sarcopenia and the evaluation of its influence on physical function and health outcomes.

Dual-energy X-ray absorptiometry (DXA) is widely recognized as the gold standard for measuring appendicular lean mass, offering a balance of validity, accessibility, and low radiation exposure compared to other modalities.

Dual-energy X-ray absorptiometry (DXA) is the most commonly used method for assessing skeletal muscle mass, particularly appendicular lean mass, due to its high validity

and widespread availability[79], [80], [81] DXA employs two distinct energy X-ray beams to differentiate lean mass from bone and fat, providing accurate estimates of appendicular skeletal muscle mass

Despite its strengths, DXA has limitations. It cannot directly measure skeletal muscle mass or assess muscle quality, as it includes connective tissue and does not distinguish between water and bone-free lean tissue[80], [81] This can lead to overestimation of muscle mass, particularly in older adults with extracellular fluid accumulation[80]

2. Bioelectrical impedance analysis (BIA):

Bioelectrical impedance analysis (BIA) is a non-invasive, cost-effective, and portable method for assessing body composition. This method includes the assessment of fat-free mass (FFM) and total body water (TBW). BIA works by measuring the impedance of a small electrical current that is passed through the body[82], [83], [84]

Introduced commercially in the mid-1980s, BIA leverages differences in electrical conductivity among tissues (e.g., muscle, fat, bone) due to their varying water content to estimate body composition parameters such as lean mass, body fat, basal metabolic rate, bioresistance, reactance, and phase angle[82], [83].

BIA has been demonstrated to be both reliable and reproducible, exhibiting strong correlations to reference methods such as DXA. However, its accuracy is constrained by the assumption that the human body is a uniform cylindrical conductor, a simplification that obscures the complex heterogeneous nature of body composition[83]

In the context of sarcopenia assessment, bioelectrical impedance analysis (BIA) has become a prevalent method among community-dwelling older adults. This approach has been shown to accurately identify muscle loss, with variables such as resistance and phase angle providing valuable insights into the assessment[83]

Research has demonstrated the efficacy of BIA in a variety of populations, including athletes, obese individuals, and oncology patients. Its applications include preoperative risk evaluation, postoperative complication reduction, and prognostic assessment[82], [84]. However, the accuracy of BIA is contingent upon stable electrolyte and fluid levels, and its validity for sarcopenia may be constrained by the absence of standardized protocols for other variables beyond skeletal muscle mass[83]. Further research is necessary to investigate the

clinical applications of BIA-derived measures, such as phase angle, in predicting outcomes such as patient survival[84]

3. Computed tomography (CT) and Magnetic Resonance Imaging (MRI):

The use of computed tomography (CT) is a common medical procedure in which a series of X-rays are taken from different angles to create a three-dimensional image of an internal body part or structure.

Computed tomography (CT) is a high-resolution imaging method that is widely regarded as the gold standard for assessing skeletal muscle mass, cross-sectional area, and quality. These assessments are determined by muscle density and intramuscular fat infiltration[81], [85]

CT differentiates skeletal muscle from bone and connective tissues, thereby enabling the concurrent measurement of muscle quantity (area) and quality (density), which reflects intramuscular adiposity linked to muscle function[81]. Lower muscle density, indicative of higher intramuscular fat content, is associated with impaired muscle function and strength[85]

However, the utilization of CT is constrained by several factors, including its high costs, operational complexity, and considerable radiation exposure. These limitations impede its application in whole-body muscle measurement in healthy individuals or large-scale studies[81], [85]. These constraints render CT less practical for routine sarcopenia screening in comparison to DXA or BIA, despite its superior accuracy in muscle quality assessment[85]

Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) is another established gold standard for skeletal muscle assessment, offering high-resolution evaluation of muscle mass, cross-sectional area, and quality without radiation exposure, a key advantage over computed tomography (CT)

The capacity of MRI to obtain multiple weighted images facilitates a more comprehensive analysis of muscle quantity and quality, including fatty degeneration, which is critical for understanding muscle function. As with CT, MRI reliably measures intramuscular fat infiltration, where lower muscle density is indicative of higher fat content, which may impair muscle performance[85]

Despite its precision, MRI is limited by high costs, operational complexity, and the need for patients to remain still for extended periods during imaging, which can be challenging for older adults. The lack of standardized reference values for diagnosing sarcopenia further restricts MRI's clinical applicability[85]. However, emerging low-field extremity MRI technologies offer less expensive alternatives, potentially increasing accessibility for muscle mass assessment in the future[81]

II.5.3. Measurement of Muscle Strength

Muscle strength assessment is a critical component of clinical evaluations, particularly for diagnosing sarcopenia and identifying functional deficits.

Dynamometry for Muscle Strength

Hand grip strength, measured using handheld dynamometers, is a reliable and validated surrogate for overall muscle strength, correlating with lower extremity measures like knee extension torque[85], [86]. In studies like the Health Aging and Body Composition cohort, low grip strength was more predictive of mobility disability and mortality than muscle mass [85]. It also predicts fall risk, frailty, and poor quality of life across diverse populations[86].

II.5.4. Assessment of physical capacity

Assessment of physical performance is essential for evaluating functional capacity in older adults

1. **Gait speed test**

Gait speed is a critical indicator of mobility, often considered a 'vital sign' of functional health in older adults. It reflects the integration of motor, sensory and cognitive functions and is strongly associated with adverse outcomes such as falls, cognitive decline, hospitalisation, disability and mortality. Gait speed is commonly assessed over short (≤15 m) or long (>15 m) distances, or for a fixed duration such as the 6-minute walk, and is fast, reliable and feasible in clinical and home settings. Standardised protocols enhance its utility by improving the detection of individuals at risk and allowing comparison between studies.[87]

The test requires subjects to wear comfortable clothing and low-heeled shoes, and minimal aids (e.g. a single stick) are encouraged to ensure valid results. Individuals who use

walkers or are unable to walk short distances unaided may be classified as having a mobility impairment, limiting the test's interpretative value for certain geriatric outcomes .[88]

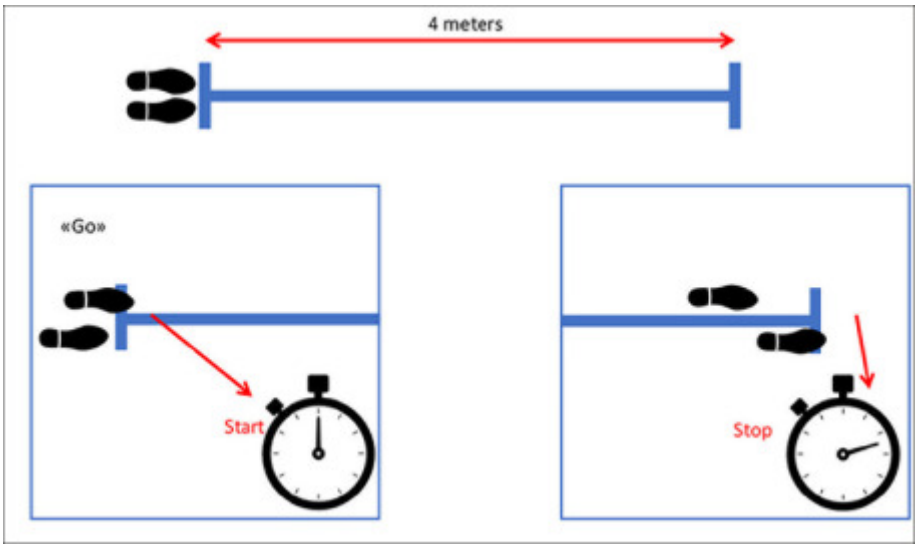

Figure 11 : meter walking test[88]

2. Short Physical Performance Battery (SPPB)

The Short Physical Performance Battery (SPPB) is a reliable, expeditious, and validated instrument for the evaluation of lower limb function through three domains: balance, strength, and gait [89], [90], [91]. The evaluation of balance is achieved through the maintenance of three progressively challenging standing positions (feet together, semi-tandem, tandem) for a duration of 10 seconds each. The assessment of strength is conducted through the implementation of the five-times sit-to-stand test, which quantifies the time required to execute five successive chair rises [89], [91]. Gait is evaluated by measuring walking speed over a distance of 3–4 metres. Each domain is scored on a scale ranging from 0 (inability) to 4 (best performance), yielding a total score of 0–12, with higher scores indicating better function (0–6: poor, 7–9: moderate, 10–12: good) [91]

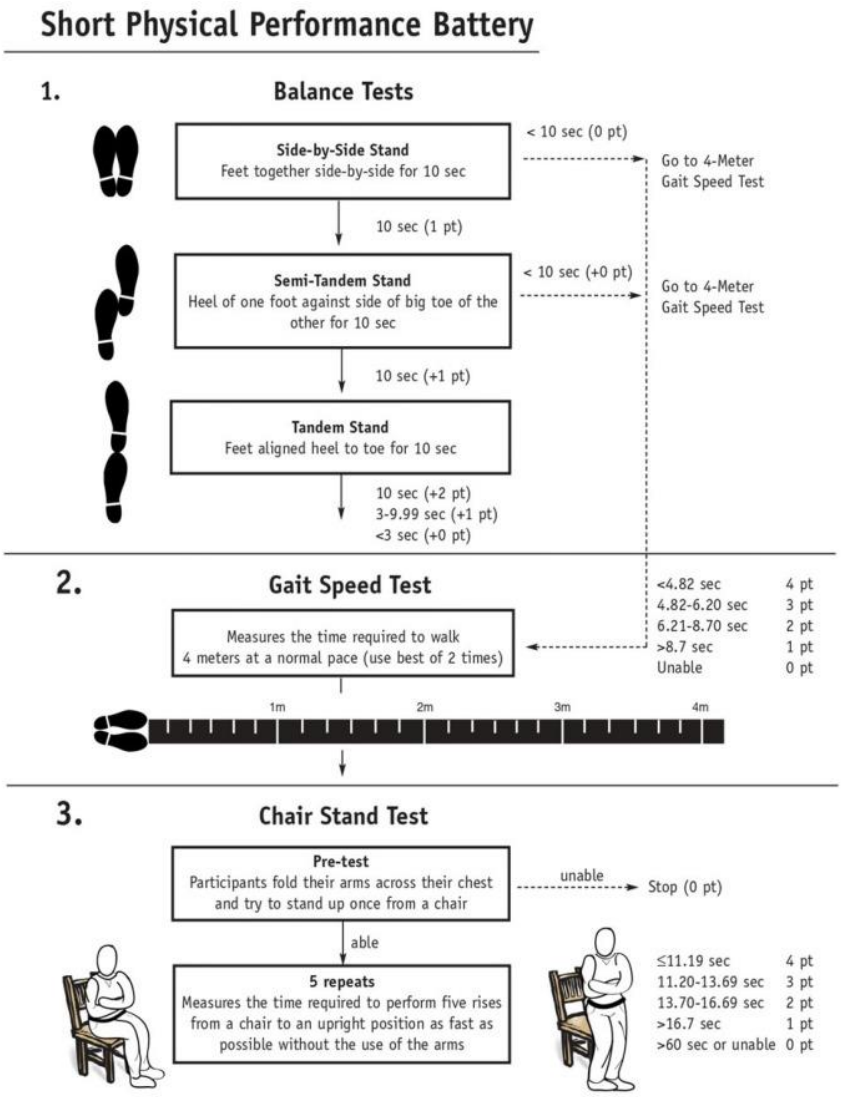

Figure 12 : short physical performance battery [91]

SPPB demonstrates sensitivity to functional decline, with a score of ≤8 exhibiting high sensitivity for sarcopenia screening, thus triggering further investigation [89]. The model has been employed to predict a range of outcomes, including falls, disability, frailty, hospitalisation and mortality. It has been utilised in various settings, including in the context of post-Covid-19 recovery. Despite the absence of specific cut-points for high sensitivity and specificity in SPPB, the integration of this tool with specific tests has the potential to enhance the diagnosis of sarcopenia[89].

Part II. Chapter 2

II.1. Introduction to Type 2 Diabetes Mellitus (T2DM)

II.1.1. Historical Perspective

Diabetes mellitus, a metabolic disorder marked by hyperglycemia due to insulin dysfunction, has a rich history spanning ancient observations to modern scientific breakthroughs.

- **Ancient Observations**

Ancient texts from Egypt (c. 1500 BCE), India (5th century BCE), and China (2nd century CE) noted diabetes symptoms like excessive thirst, frequent urination, and sweet urine. Egyptian papyri vaguely described such conditions, while Indian physician Sushruta termed it madhumeha ("honey urine"), linking it to diet. Chinese physicians like Chen Chuan identified sweet urine and proposed dietary restrictions[92]

- **Greco-Roman and Medieval Insights**

In the 2nd century CE, Aretaeus of Cappadocia coined "diabetes," describing it as a "melting down of flesh into urine" with unquenchable thirst and rapid decline. He suggested treatments like cereals and wine [92] Medieval physicians Avicenna (980–1037 CE) and Maimonides (1138–1204 CE) documented complications like gangrene and acidosis, prescribing seed mixtures [93]

- **Early Modern Advances**

In 1679, Thomas Willis added mellitus to describe sweet urine, attributing diabetes to diet and stress, and recommended vegetables and milk-based remedies [93], [94] John Rollo formalized mellitus in 1798 to distinguish it from diabetes insipidus[92]

- **19th-Century Breakthroughs**

Claude Bernard (1813–1878) discovered the liver’s glycogenic role, identifying glycogen and linking glucose homeostasis to the brain via "piqûre diabétique" experiments [3]. In 1889, Oskar Minkowski and Joseph von Mering induced diabetes in dogs by removing the pancreas, proving its endocrine role [3].

- **Insulin and Modern Diabetology**

The discovery of insulin in the early 20th century marked a pivotal moment in diabetes treatment. The following elements outline the key events in chronological order, tracing the development from experimental research to clinical application and recognition. [93]

- **Experimental Foundation (1921)**

In 1921, Frederick Banting and Charles Best, working under John Macleod at the University of Toronto, built on Oskar Minkowski's and Joseph von Mering's earlier findings. They ligated pancreatic ducts in dogs to atrophy the exocrine pancreas and extracted a substance from the degenerated tissue. When administered to depancreatized dogs, this extract significantly reduced blood sugar levels[93]

Figure 13 : The Nobel laureate Frederick Banting in his laboratory with a dog[93]

- **Refinement of Insulin (Late 1921)**

James Collip joined the team and refined the extraction process, producing a purer substance that was named insulin. This improvement enhanced the substance's efficacy and safety for potential human use[93]

- **First Human Administration (January 11, 1922)**

On January 11, 1922, insulin was first administered to a human, 14-year-old Leonard Thompson. The treatment dramatically lowered his blood glucose levels and eliminated urinary ketones, transforming diabetes from a fatal condition to a manageable one[93]

- **Commercial Production (1923)**

In 1923, Lilly Pharmaceutical Company collaborated with the researchers to introduce Iletin, the world's first commercially available insulin product. This marked the dawn of modern diabetology, making insulin widely accessible and saving millions of lives[93]

- **Nobel Prize and Controversy (1923)**

The 1923 Nobel Prize in Medicine was awarded to Frederick Banting and John Macleod for the discovery of insulin. The decision sparked controversy, as Banting believed Charles Best deserved recognition and shared his prize money with him, while Macleod shared his with James Collip [93]

II.1.2. Current Definition and Diagnostic Criteria:

1. **Definition** :

Type 2 Diabetes Mellitus (T2DM) is a prevalent metabolic disorder, the aetiology of which is multifactorial

Type 2 diabetes mellitus (T2DM), accounting for approximately 90% of all diabetes cases, is characterised by insulin resistance, whereby the body's response to insulin is diminished, rendering it ineffective.[95]

Initially, the pancreas compensates by increasing insulin production to maintain glucose homeostasis. However, with the passage of time, there is a decline in the body's ability to produce insulin, resulting in elevated blood sugar levels and the subsequent development of T2DM [95]. This heterogeneous disorder is characterised by impaired insulin secretion and action, resulting in chronic hyperglycaemia [96].

2. **Clinical Implications**

The severity of T2DM varies, with some individuals achieving good control while others face progressive health complications. The chronic hyperglycemia in T2DM is associated with a reduced life expectancy due to an increased risk of serious conditions, including heart disease, stroke, peripheral neuropathy, renal disease, blindness, and amputation[96], [97]

3. Diagnostic Criteria:

The ADA specifies the following criteria for diagnosing T2DM in nonpregnant individuals, with diagnosis confirmed by any one of the following [98], [99]

- **Fasting Plasma Glucose (FPG):**

  FPG ≥126 mg/dL (7.0 mmol/L) after an 8-hour fast.

- **2-Hour Plasma Glucose (2-h PG)**

  2-h PG ≥200 mg/dL (11.1 mmol/L) during a 75-g OGTT.

- **Random plasma glucose** ≥200 mg/dL (11.1 mmol/L) with classic hyperglycemic symptoms or crisis.

- **Hemoglobin A1c (HbA1c)**

  A1C ≥6.5% (48 mmol/mol) using a certified assay.

II.1.3. Epidemiology and Global Burden

1. Global Prevalence and Incidence

Type 2 diabetes mellitus (T2DM) accounts for over 90% of all diabetes cases on a global scale. It is one of the most prevalent and rapidly growing chronic conditions worldwide, affecting a vast range of populations. In 2024, it was estimated that 589 million adults aged 20–79 years were living with diabetes, and this number is projected to rise to 853 million by 2050 (Ibid.). This figure denotes a 45% global increase, underscoring the pressing need for the implementation of prevention and control strategies targeting high-risk demographics[100]

Figure 14 : Global Prevalence of Type 2 diabetes [100]

2. Age and Demographic Distribution

The prevalence of T2DM is notably high among individuals aged 40 to 59 years, which represents the majority of the global diabetic population. Moreover, recent trends indicate a concerning escalation in the prevalence of obesity among younger adults and adolescents, largely attributable to the increasing prevalence of obesity and sedentary lifestyles. The disease burden is found to be disproportionately higher in low- and middle-income countries, with over 75% of people with diabetes residing in these countries[100] This phenomenon can be attributed to inequalities in health systems and prevention efforts.

3. Geographical Variations and Trends

There are significant regional variations in the prevalence of T2DM. In 2024, the Western Pacific region was found to have the highest number of diabetes cases, with 215.4 million cases recorded. This was followed by South-East Asia, with 106.9 million cases, and Europe, with 65.6 million cases. Despite the fact that Africa is currently the least affected region, with a prevalence of 24.6 million, it is projected to undergo the most significant relative increase, with the number of people with diabetes expected to reach 59.5 million by 2050. This represents an increase of 142% [100]

The Middle East and North Africa (MENA) region has also been observed to demonstrate notably elevated prevalence levels, with projections indicating an escalation

from 84.7 million in 2024 to 162.6 million in 2050, signifying a substantial 92% surge. The aforementioned figures serve to emphasise the impact of socioeconomic, cultural and environmental factors across diverse populations and regions.[100]

4. Lifestyle and Environmental Risk Factors

The rise in T2DM prevalence is driven largely by modifiable lifestyle factors. Urbanization, economic growth, and technological advancement have resulted in more sedentary behavior, increased consumption of energy-dense foods, and greater exposure to air pollution. These environmental and lifestyle changes significantly elevate the risk of developing insulin resistance and, consequently, type 2 diabetes. Moreover, factors such as overweight and obesity, physical inactivity, and unhealthy diets (rich in sugar-sweetened beverages, refined carbohydrates, and saturated fats) are consistently linked to T2DM incidence [100]

5. Future Projections and Healthcare Burden

According to projections, by 2050, approximately 852.5 million people globally will be living with diabetes. This staggering number reflects a 45% increase from the 2024 estimate. Notably, Africa is expected to face the most dramatic surge (142%), followed by South-East Asia and MENA (73% and 92%, respectively). The economic burden is also increasing: direct health expenditures on diabetes surpassed USD 1 trillion in 2024, a milestone that signals rising costs for governments and individuals alike[100]

The growing prevalence also contributes to higher diabetes-related mortality. In 2024, more than 3.4 million people aged 20–79 years died due to complications of diabetes, particularly cardiovascular and renal complications. Furthermore, about 43% of diabetes cases remain undiagnosed, most of which are type 2, emphasizing the critical need for enhanced screening and early intervention strategies[100]

6. Prevalence of Type 2 Diabetes in Algeria

In 2024, Algeria recorded an estimated 4.76 million adults (aged 20–79 years) living with diabetes, with a national prevalence of 16.9% and an age-adjusted rate of 17.5%. It is estimated that approximately 31.7% of cases remain undiagnosed, indicative of substantial deficiencies in the efficacy of early detection systems. In that particular year, the nation also documented 20,642 fatalities attributable to diabetes. The economic burden of the disease was calculated to be USD 3.1 billion, with an average cost of USD 653 per patient.

Moreover, the presence of prediabetic conditions, including impaired glucose tolerance (6.5%) and impaired fasting glucose (6.8%), underscores an escalating population at risk[100]

II.2. Pathophysiology of Type 2 Diabetes Mellitus

II.2.1. Insulin Resistance:

II.2.1.1. Definition of Insulin

Insulin is a 51-amino-acid peptide hormone, anabolic in nature, secreted by pancreatic β-cells in the islets of Langerhans, which regulates glucose homeostasis, carbohydrate, lipid, and protein metabolism, and promotes cell growth and division through mitogenic effects [101], [102]

II.2.1.2. Biochemical Composition

Insulin consists of two chains (A and B) connected by disulfide bonds, derived from a single-chain precursor, proinsulin, through post-translational processing .[103]

II.2.1.3. Synthesis in Pancreatic β-Cells

Synthesized in the β-cells of the pancreatic islets of Langerhans, insulin production is regulated by β-cells monitoring plasma levels of glucose, amino acids, keto acids, and fatty acids to meet metabolic demands[104]

II.2.1.4. Metabolic and Physiological Functions

Insulin, an anabolic hormone, plays a central role in regulating human metabolism by facilitating energy conservation and utilization during feeding and fasting states[104], [103] . Its primary functions include stimulating glucose uptake from systemic circulation and suppressing hepatic gluconeogenesis, thereby maintaining glucose homeostasis [4]. Additionally, insulin regulates carbohydrate, lipid, and protein metabolism while promoting cell division and growth through its mitogenic effects[101] . These actions collectively ensure efficient nutrient storage and utilization across metabolic tissues [101], [104]

II.2.1.5. Mechanisms of Insulin Action:

1. Activation of Insulin Receptors

The insulin receptor (IR) is a heterotetramer made up of two transmembrane β subunits and two extracellular α subunits connected by disulfide bonds. Important tyrosine residues (Tyr-1158, Tyr-1162, and Tyr-1163) are autophosphorylated when insulin binds to the α subunit,

activating the intrinsic tyrosine kinase of the β subunit. For downstream signaling cascades essential to insulin's metabolic and growth-promoting roles, this event serves as the main trigger[105]

2. IRS Branching into Two Main Pathways and Phosphorylation

Insulin receptor substrate (IRS) proteins, particularly IRS-1, are recruited and phosphorylated by autophosphorylated IR, and these phosphotyrosine sites act as docking sites for adaptor proteins like GRB2 and enzymes like PI3K.

This bifurcates the signal into two essential pathways:

- The **PI3K/Akt pathway**, which governs metabolic responses
- The **MAPK/ERK pathway**, which regulates cell proliferation and survival[102], [105]

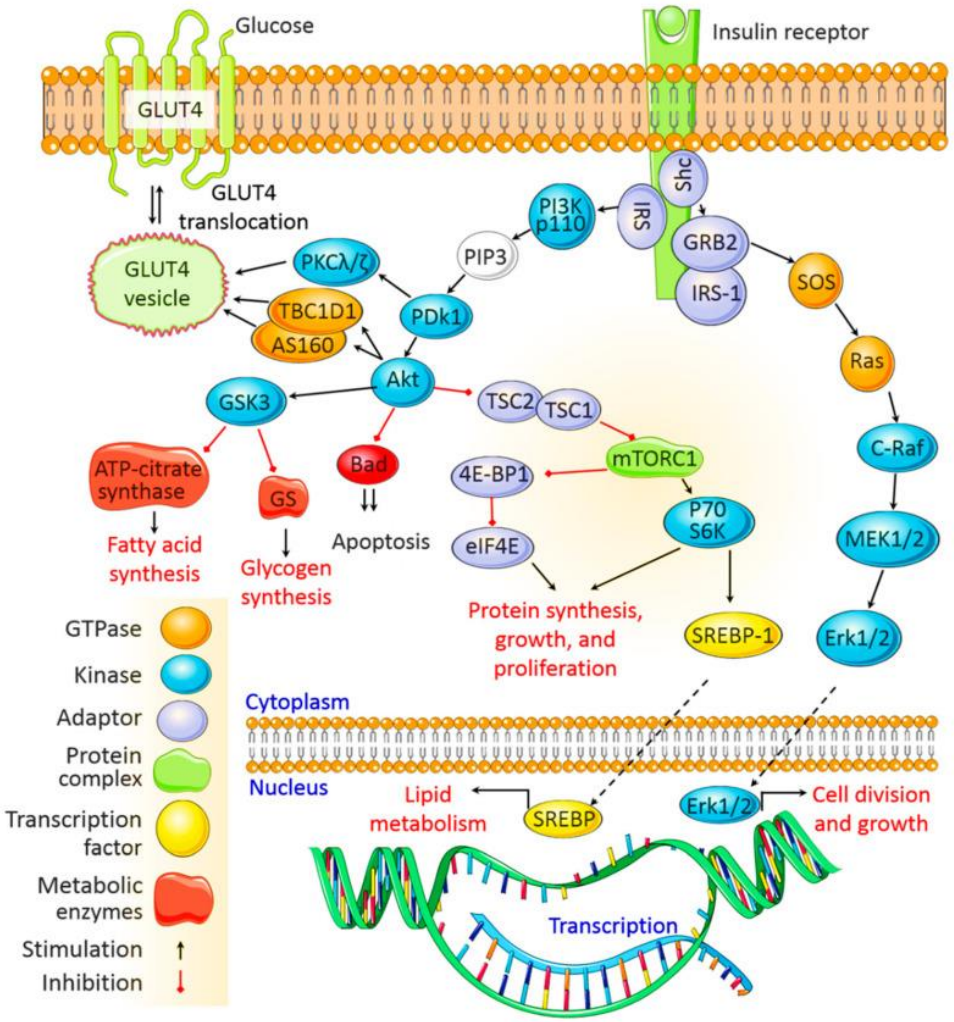

Figure 15 : *Classic insulin signaling pathway*[102]

3. PI3K/Akt Pathway and Metabolic Effects

PIP3 Production and I3K Activation

IRS enlists PI3K, a lipid kinase that has two subunits: a catalytic subunit (p110) and a regulatory subunit (p85). PIP2, a secondary messenger that attracts proteins with pleckstrin homology (PH) domains, such as PDK1 and Akt (Protein Kinase B), to the plasma membrane, is transformed into PIP3 by activated PI3K[105]

4. Downstream Metabolic Functions and Akt Activation

Akt is phosphorylated by PDK1 and mTORC2. Then, in order to control cellular metabolism, activated Akt phosphorylates several substrates:

GLUT4 translocation: GLUT4 vesicle fusion with the membrane is facilitated by Akt's phosphorylation of AS160/TBC1D1, which also increases glucose uptake **Glycogen synthesis**: GSK3 inhibition by Akt releases its inhibition of glycogen synthase (GS), improving glycogen storage.

Fatty acid synthesis: Akt facilitates ATP-citrate lyase activation, which produces cytosolic acetyl-CoA for lipogenesis.

Inhibition of apoptosis: Akt phosphorylates and inhibits the pro-apoptotic protein Bad.

Protein synthesis and growth: Akt inhibits **TSC1/2**, activating **mTORC1**, which then phosphorylates:

- **4E-BP1**, releasing **eIF4E** to initiate mRNA translation.
- **S6 kinase (p70S6K)**, enhancing protein synthesis.

mTORC1 also activates **SREBP-1**, a transcription factor that upregulates genes involved in **lipid metabolism**[102], [105]

MAPK/ERK Pathway and Proliferative Effects

5. GRB2–SOS–Ras Axis and ERK Activation

Simultaneously, IRS-bound GRB2 recruits SOS, which activates the GTPase **Ras**. Ras initiates a kinase cascade involving **C-Raf → MEK1/2 → ERK1/2 (MAPKs)**. Activated ERK translocates to the nucleus, where it stimulates transcription of genes involved in **cell cycle progression, differentiation, and proliferation**[102]

6. Nuclear Transcriptional Regulation

- **SREBP**, activated by mTORC1, enters the nucleus and promotes the transcription of genes involved in **lipogenesis**.
- **ERK1/2**, after nuclear entry, activates transcription factors involved in **cell growth and division**.
- These combined actions ensure the coordinated regulation of **energy storage**, **cell survival**, and **growth** in response to insulin signaling.[105]

II.2.1.6. Insulin resistance

Insulin resistance (IR) is defined as an impaired biological response of insulin-sensitive tissues, primarily liver, skeletal muscle, and adipose tissue, to insulin stimulation, resulting in reduced metabolic responsiveness to circulating insulin and impaired glucose disposal[106]

This condition leads to compensatory hyperinsulinemia due to increased β-cell insulin production and can arise from diminished insulin secretion, insulin antagonists (e.g., counter-regulatory hormones like glucagon, glucocorticoids, or catecholamines), or defective insulin signaling in target tissues, often preceding systemic IR and type 2 diabetes mellitus[107]

II.2.1.7. Mechanisms and Pathophysiology of Insulin Resistance:

1. Defects in Insulin Receptor Signaling

IR in skeletal muscle, liver, and adipose tissue is associated with reduced insulin receptor tyrosine kinase (IRTK) activity, impairing phosphorylation of insulin receptor substrates (IRS1/IRS2)

Mutations or environmental factors reducing IRTK expression or phosphorylation sites (e.g., Thr1160 in liver, Ser1101 in muscle) disrupt insulin signaling, decreasing glucose uptake and metabolic regulation [108]

2. Post-Receptor Signaling Abnormalities (PI3K/Akt Pathway)

Impaired IRS1/IRS2 phosphorylation reduces PI3K activity, limiting phosphatidylinositol-3,4,5-trisphosphate (PIP3) production and Akt activation in skeletal muscle, liver, and adipose tissue

. This disrupts glucose transporter type 4 (GLUT4) translocation, glycogen synthesis, and gluconeogenesis suppression, contributing to hyperglycemia. Selective insulin resistance in the liver allows Akt-mediated lipogenesis via SREBP-1c while failing to suppress gluconeogenesis, exacerbating hyperglycemia and hepatic steatosis[108]

3. Role of Intracellular Lipid Accumulation (Lipotoxicity)

Ectopic lipid accumulation, particularly diacylglycerol (DAG) and ceramides, in skeletal muscle and liver is a primary driver of IR. In muscle, DAG activates protein kinase C theta (PKCθ), phosphorylating IRS1 at Ser1101, reducing insulin-stimulated glucose uptake. In the liver, DAG activates PKCε, inhibiting IRTK and downstream IRS2/PI3K/Akt2 signaling, impairing gluconeogenesis suppression. Ceramides impair Akt translocation via atypical PKCζ or PP2A activation, further disrupting insulin signaling. Lipodystrophy models highlight that ectopic lipid deposition in non-adipose tissues causes severe IR[108]

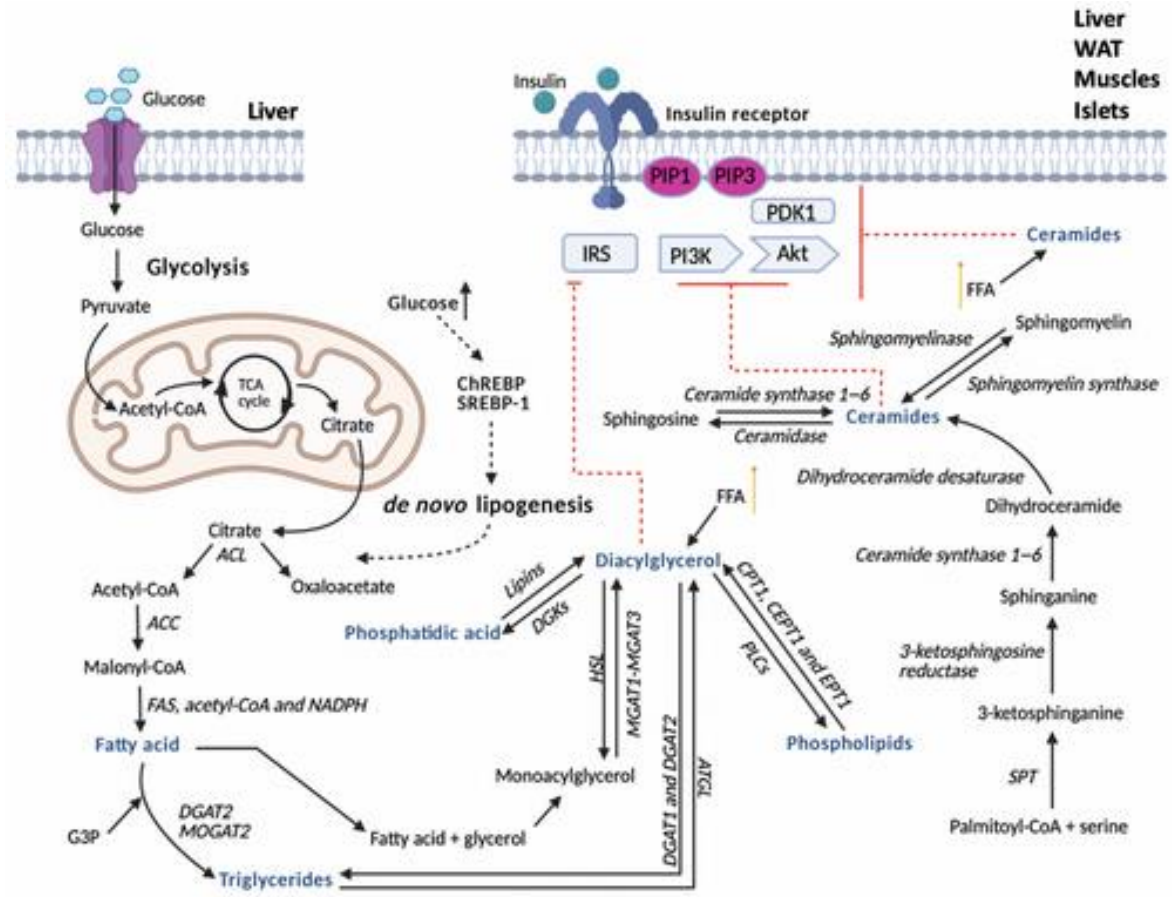

Figure 16 : *Molecular mechanisms of lipid-induced insulin resistance across metabolic tissues*[109]

4. Impact of Endoplasmic Reticulum (ER) Stress

ER stress is implicated in IR through its association with lipid accumulation and inflammation [107]Excessive FFAs and hyperglycemia activate unfolded protein response (UPR) pathways, contributing to β-cell dysfunction and impaired insulin signaling in metabolic tissues[107]

5. Influence of Inflammatory Cytokines

Chronic low-grade inflammation, driven by proinflammatory cytokines (e.g., TNF-α, IL-6, IL-1β) from hypertrophic adipocytes and immune cells, exacerbates IR.

In skeletal muscle, inflammation impairs myocyte metabolism via paracrine effects, reducing glucose uptake. In adipose tissue, cytokines promote lipolysis and FFA release, worsening systemic IR and hepatic gluconeogenesis[109]

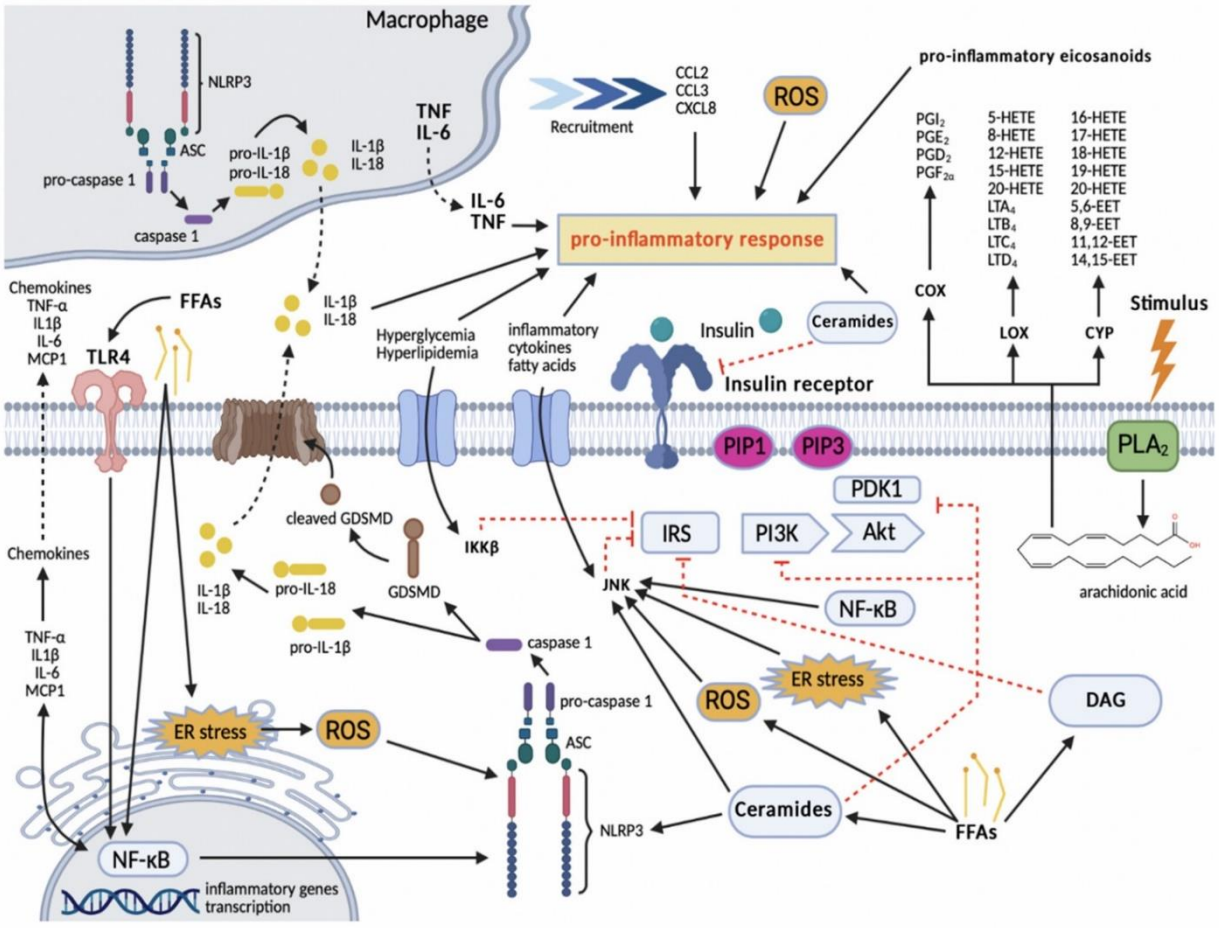

Figure 17 : *Inflammatory and cellular stress-related pathways contributing to insulin resistance*[109]

6. Contribution of Mitochondrial Dysfunction

Mitochondrial dysfunction, linked to obesity and T2DM, promotes IR via reactive oxygen species (ROS) overproduction, which damages proteins, DNA, and lipids, impairing insulin signaling. Reduced mitochondrial biogenesis (downregulated PGC-1α, mitofusin-2) and impaired mitophagy increase lipid intermediates (DAG, ceramides), disrupting IRS1 and Akt signaling in skeletal muscle and liver. Mitochondrial DNA variants (e.g., A3243G) further predispose to IR[107]

II.2.1.8. Target Tissue Dysfunction :

Skeletal Muscle

Insulin resistance in skeletal muscle, accounting for ~70% of glucose disposal, impairs glucose uptake due to defective GLUT4 translocation caused by disrupted insulin signaling (IRTK, IRS1, PI3K, Akt) Diacylglycerol (DAG) accumulation activates PKCθ, inhibiting IRS1, while the hexosamine biosynthesis pathway (HBP) impairs signaling via O-GlcNAcylation. Obesity-driven inflammation exacerbates resistance[107]

Liver

Hepatic insulin resistance increases hepatic glucose production (HGP) via unsuppressed gluconeogenesis (FOXO1 activation) and reduces glycogen synthesis, causing hyperglycemia Selective insulin resistance promotes lipogenesis (SREBP-1c) but not HGP suppression. DAG activates PKCε, impairing IRTK and downstream signaling, while ceramides inhibit Akt. Excess FFAs from adipose lipolysis fuel gluconeogenesis[107]

Adipose Tissue

Adipose insulin resistance (adipose-IR) reduces glucose uptake and lipolysis suppression, elevating FFAs, which worsen resistance in muscle and liver. Defective Akt impairs GLUT4 translocation and enhances lipolysis. DAG disrupts signaling via PKCs, and HBP contributes through O-GlcNAcylation. Obesity-induced inflammation and hypoxia aggravate adipose-IR[107]

II.2.2. Pancreatic Beta-Cell Dysfunction :

II.2.2.1. B-Cell Physiology

Insulin is produced by pancreatic β-cells and is first synthesized as pre-proinsulin, which is then converted to proinsulin by conformational changes in the endoplasmic

reticulum (ER), cleaved into mature insulin and C-peptide in the Golgi apparatus, and then stored in granules. Elevated glucose levels mainly cause insulin release through glucose transporter 2 (GLUT2), which raises the ATP/ADP ratio, depolarizes the membrane, closes ATP-dependent potassium channels, and opens voltage-dependent Ca2+ channels, which causes Ca2+ influx and insulin exocytosis. Through Ca^{2+}-induced Ca^{2+} release, ryanodine receptors (RYR) enhance Ca^{2+} signals. Insulin release is further enhanced by other signals, such as cAMP, which mobilizes Ca2+ reservoirs, and extracellular ATP, which acts through P2Y and P2X purinergic receptors to enhance Ca2+ mobilization[107]

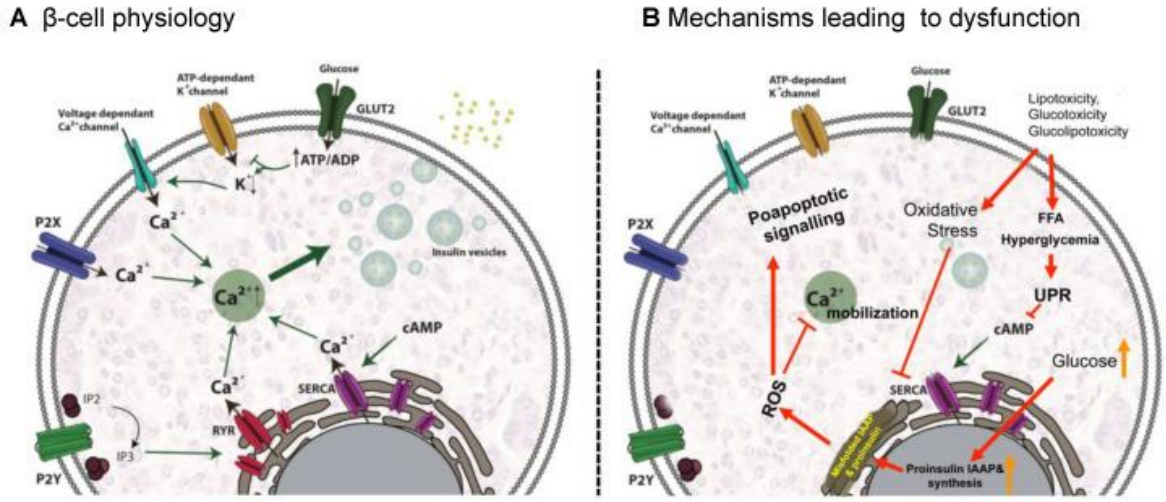

Figure 18 : *Signaling pathways involved in insulin secretion in-cells in physiological conditions (A) and mechanisms leading to dysfunction (B)*[107]

II.2.2.2. Mechanisms of β-Cell Dysfunction

β-Cell dysfunction in type 2 diabetes mellitus (T2DM) arises from a complex interplay of environmental and molecular factors, including glucotoxicity, lipotoxicity, and inflammatory stress, rather than solely β-cell death

. Chronic hyperglycemia (glucotoxicity) depletes insulin secretory granules, reducing insulin availability, while high fatty acid levels (lipotoxicity) impair β-cell function and restrict proliferation by inducing cell cycle inhibitors P16 and P18, particularly under hyperglycemia. Excess free fatty acids (FFAs) and glucose induce ER stress via apoptotic unfolded protein response (UPR) pathways, disrupting ER Ca^{2+} homeostasis, increasing proinsulin and islet amyloid polypeptide (IAAP) misfolding, and generating reactive oxygen species (ROS). These stressors promote proapoptotic signals, proinsulin mRNA degradation, and interleukin-1β (IL-1β) release, enhancing local islet inflammation and macrophage recruitment. Reduced β-cell mass, approximately halved in T2DM patients, and increased

apoptosis with disease duration further impair insulin response. Low-grade inflammation and disrupted islet integrity impair cell-to-cell communication, exacerbating dysregulated insulin and glucagon release, contributing to hyperglycemia. Defects in GLUT2 expression or proinsulin folding also hinder insulin production and secretion, driving β-cell failure and T2DM progression [107], [110].

II.2.3. Role of Other Hormones and Factors:

II.2.3.1. Incretins (GLP-1 and GIP)

II.2.3.1.1. Definition

Incretins are intestinal hormones, primarily glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), released in response to nutrient ingestion, which potentiate glucose-induced insulin secretion from pancreatic β-cells[111]

GIP, a 42-amino-acid hormone, is secreted by K-cells in the upper small intestine, while GLP-1, a 31-amino-acid hormone, is produced by L-cells in the distal intestine and colon, with additional secretion from pancreatic α-cells and hypothalamic neurons. Both are rapidly degraded into inactive metabolites by dipeptidyl peptidase-4 (DPP-4)[112]

II.2.3.1.2. Function

GIP: GIP, responsible for ~60% of the incretin effect, is released postprandially in response to fats and carbohydrates, stimulating insulin secretion in a glucose-dependent manner, with no insulin release during euglycemic fasting to prevent hypoglycemia . [111] It promotes β-cell proliferation, inhibits apoptosis, enhances postprandial glucagon response, facilitates fat deposition in adipose tissue, promotes bone formation, and supports memory and appetite control in the brain. GIP binds to GIP receptors (GIPR), increasing cyclic adenosine monophosphate (cAMP) levels in β-cells to enhance insulin secretion[112]

GLP-1: GLP-1, a potent insulinotropic hormone, is secreted after meals, particularly carbohydrates, and stimulates insulin release while inhibiting glucagon secretion, hepatic glucose production, gastric emptying, and appetite, inducing satiety. It promotes β-cell proliferation, inhibits apoptosis, and suppresses glucagon response, with preserved insulinotropic effects in type 2 diabetes mellitus (T2DM) despite reduced postprandial GLP-1 levels. GLP-1 binds to GLP-1 receptors (GLP-1R), elevating cAMP to stimulate glucose-dependent insulin secretion, and inhibits bone resorption while supporting memory and

appetite regulation in the brain [112]. Its effects on postprandial glucose are partly mediated by neural or endocrine mechanisms triggered by luminal glucose sensing[113]

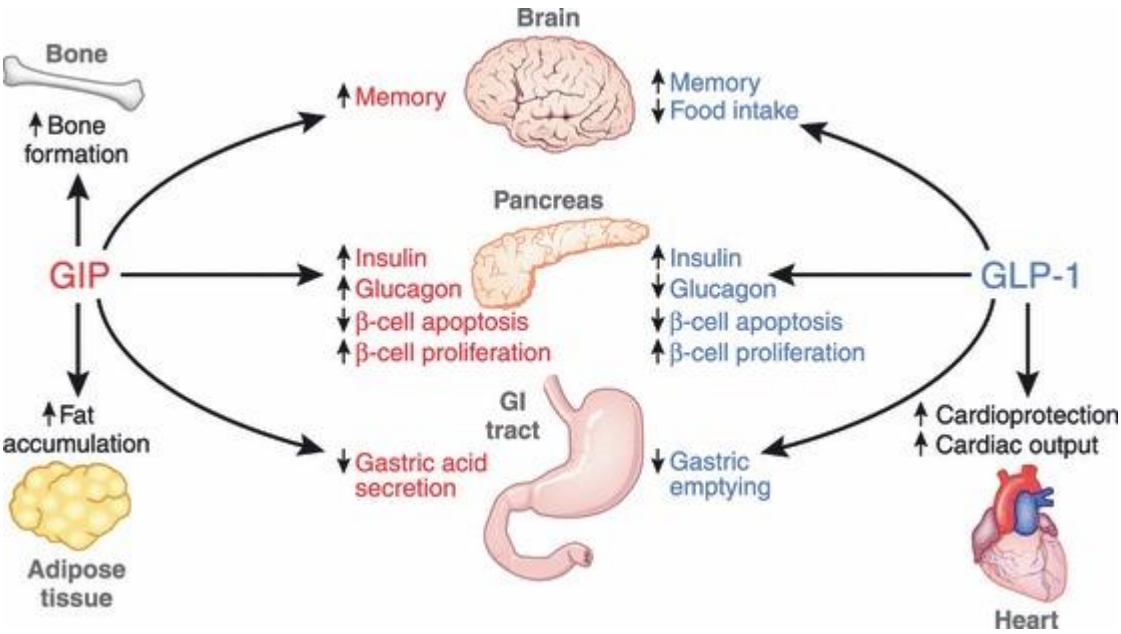

Figure 19 : *Pancreatic and exopancreatic function of glucose-dependent insulinotropic polypepide (GIP) and glucagon-like peptide (GLP)-1*[113]

II.2.3.1.3. Pathophysiology of Incretins (GLP-1 and GIP) in Type 2 Diabetes Mellitus

Impaired GIP Function in T2DM

In T2DM, the insulinotropic effect of glucose-dependent insulinotropic polypeptide (GIP) is significantly diminished, potentially due to genetically determined reduced expression of β-cell GIP receptors (GIPR), which may be an early step in disease pathogenesis or a consequence of chronic hyperglycemia. This reduced GIP responsiveness limits its ability to stimulate insulin secretion, contributing to impaired glucose homeostasis, despite GIP secretion levels remaining relatively normal. The loss of GIP's insulinotropic action reduces its therapeutic potential in T2DM, as β-cells become refractory to GIP stimulation[111]

GLP-1 Deficiency and Preserved Function

Glucagon-like peptide-1 (GLP-1) exhibits a significant postprandial secretion deficit in T2DM, with reduced plasma GLP-1 responses compared to individuals with normal glucose tolerance, and an intermediate response in those with impaired glucose tolerance

(IGT). This deficit, which correlates with the degree of obesity, impairs GLP-1's ability to stimulate insulin secretion, inhibit glucagon release, slow gastric emptying, and suppress appetite, exacerbating hyperglycemia. Unlike GIP, GLP-1's insulinotropic effects remain well-preserved in T2DM, even when β-cells are unresponsive to other stimuli, making GLP-1 a promising therapeutic target. The reasons for preserved GLP-1 action are unclear but have significant clinical implications[111]

Incretin Effect and β-Cell Dysfunction

The incretin effect, mediated primarily by GIP and GLP-1, is impaired in T2DM due to reduced GIP responsiveness and deficient GLP-1 secretion, leading to inadequate glucose-dependent insulin secretion from pancreatic β-cells . [113] This contributes to β-cell dysfunction, a hallmark of T2DM, as the combined loss of GIP's insulinotropic action and reduced GLP-1 levels fails to adequately potentiate insulin release in response to nutrient ingestion. The rapid degradation of both GIP and GLP-1 by dipeptidyl peptidase-4 (DPP-4) further limits their insulinotropic effects, exacerbating β-cell dysfunction and hyperglycemia in T2DM[113]

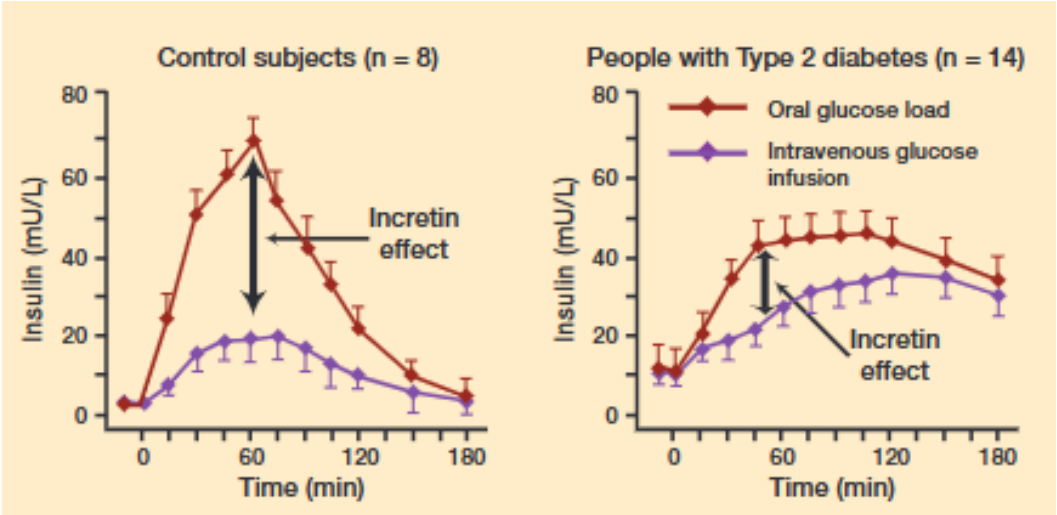

Figure 20 : *: Incretin effect on insulin secretion*[111]

II.2.3.2. Glucagon

Definition

Glucagon is a 29-amino-acid peptide hormone secreted by pancreatic α-cells, with a potent stimulatory effect on hepatic glucose production, acting as the primary counter-regulatory hormone to insulin to maintain glucose homeostasis[114]

Physiology

Glucagon is secreted in response to low plasma glucose levels (hypoglycemia), promoting glycogenolysis and gluconeogenesis in the liver while inhibiting glycogenesis, thus mobilizing glucose into circulation. It also influences lipid metabolism, food intake, body weight, autophagy, cardiovascular function, and amino acid metabolism via hepatic ureagenesis. Glucagon secretion is modulated by factors like GLP-1 (inhibitory) and may occur extrapancreatically, potentially from enteroendocrine cells . In pancreatic islets, glucagon acts paracrinally on β-cells, and an altered α- to β-cell ratio may impact glucose regulation . [114]

Pathophysiology in T2DM

In type 2 diabetes mellitus (T2DM), glucagon regulation is defective, leading to hyperglucagonemia in fasting and postprandial states, with failure to suppress or paradoxical increases in glucagon levels after meals, exacerbating hepatic glucose output and hyperglycemia . This may result from α-cell resistance to glucose and insulin's suppressive effects or gut-derived glucagon secretion triggered by oral glucose intake, unlike intravenous glucose, which suppresses glucagon. The "bihormonal hypothesis" suggests that relative hyperglucagonemia, combined with hypoinsulinemia, drives diabetic hyperglycemia . Potential β-cell dedifferentiation to glucagon-producing cells or altered α- to β-cell ratios may contribute to T2DM pathogenesis .[115]

II.2.3.3. Gut Microbiota:

Definition

The gut microbiota comprises diverse microorganisms, including bacteria, fungi, archaea, viruses, and protozoans, predominantly Firmicutes and Bacteroidetes, residing in the gastrointestinal tract . It plays a critical role in nutrient metabolism, pathogen protection, and immune system modulation[116]

Physiology

The gut microbiota maintains mucosal barrier integrity, produces short-chain fatty acids (SCFAs) to regulate energy metabolism, immune responses, and appetite, and protects against pathogens by competing for attachment sites and inducing antimicrobial compounds . Beneficial genera like Bifidobacterium, Bacteroides, Roseburia, Faecalibacterium, and Akkermansia enhance glucose metabolism, reduce inflammation, and improve gut permeability, while SCFAs modulate gut hormones (e.g., GLP-1) and fatty acid oxidation .

Diet, particularly high-fat or high-carbohydrate intake, shapes microbiota composition, with Bacteroides-dominant enterotypes linked to high-fat/protein diets and Prevotella-dominant to high-carbohydrate diets[117]

Pathophysiology in T2DM

Gut microbiota dysbiosis in T2DM is characterized by reduced abundance of beneficial bacteria (e.g., Bifidobacterium, Bacteroides, Akkermansia) and increased pathogenic bacteria (e.g., Lactobacillus, Ruminococcus), contributing to insulin resistance, inflammation, and metabolic disorders[116]

. In T2DM patients, lower levels of butyrate-producing Clostridium and higher Lactobacillus correlate with elevated fasting glucose and HbA1c. Dysbiosis, driven by high-fat/high-sugar Western diets, increases gut permeability, metabolic endotoxemia, and proinflammatory cytokines, exacerbating β-cell dysfunction via reactive oxygen species and ER stress . Beneficial microbes reduce inflammation (e.g., via IL-10 induction), enhance gut barrier function, and improve glucose homeostasis, while pathobionts like Fusobacterium promote inflammation.[118]

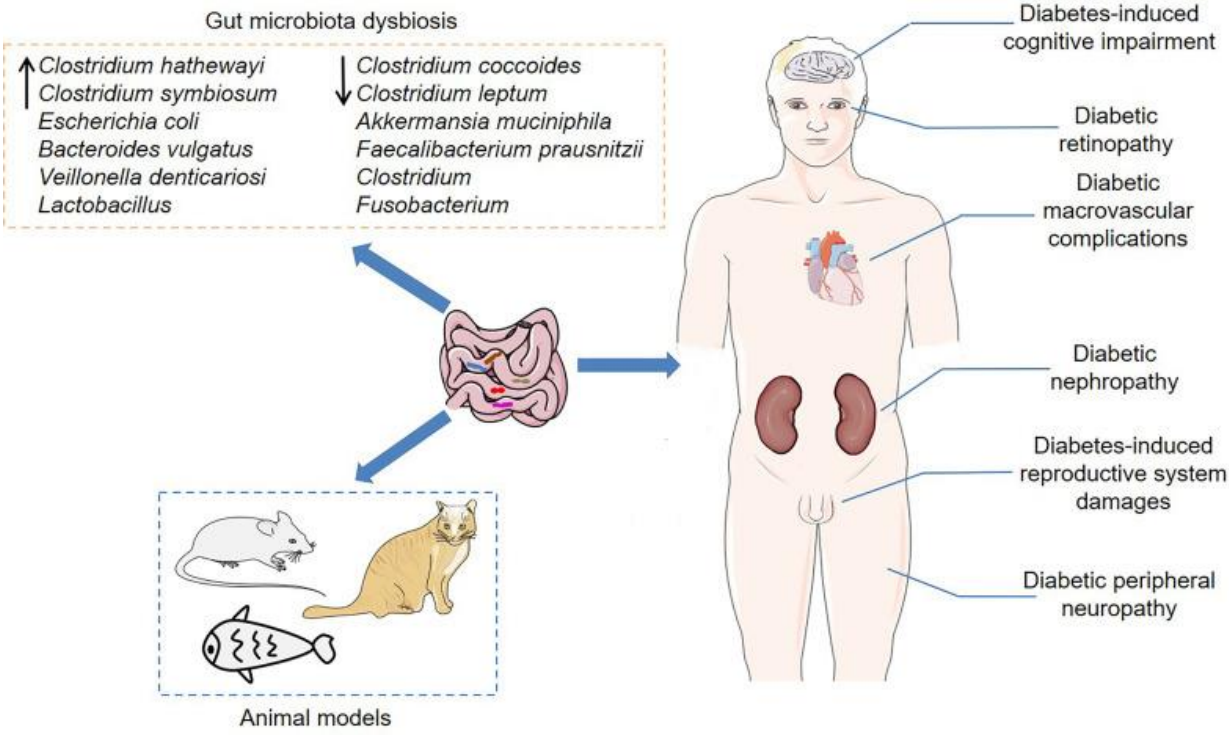

Figure 21 : *The association between the gut microbiota and T2DM*[119]

II.3. Risk Factors for Type 2 Diabetes Mellitus

II.3.1. Non-Modifiable Risk Factors:

II.3.1.1. Age :

Aging significantly increases type 2 diabetes mellitus (T2DM) risk by impairing insulin secretion and increasing insulin resistance through obesity and sarcopenia . Older age reduces physical activity, worsening risk, particularly in those ≥65 years[119] . T2DM incidence rises after age 30, independent of lifestyle, with recent increases in younger adults (30–49 years) linked to obesity and inactivity[120], [121]. Undiagnosed cases are common among older adults, especially in home care settings[119]

II.3.1.2. Family History and Genetics:

Family history significantly increases type 2 diabetes mellitus (T2DM) risk, with a 3.5-fold higher risk for offspring with one diabetic parent and a 6-fold higher risk with two, supported by near 100% concordance in identical twins and familial aggregation [121]. No specific T2DM gene is identified, but ethnic and racial predispositions underscore genetic influence, with maternal transmission linked to milder glucose intolerance than paternal[121]

Genetic variations interact with environmental factors, modulating T2DM risk through gene-environment interactions . For instance, the GCKR variant interacts with whole grain intake to affect fasting insulin, while the SLC30A8 variant’s glucose-raising effect is attenuated by zinc intake . Higher genetic risk scores, based on multiple polymorphisms, amplify T2DM risk with increased BMI, though lifestyle interventions can mitigate this risk[120]

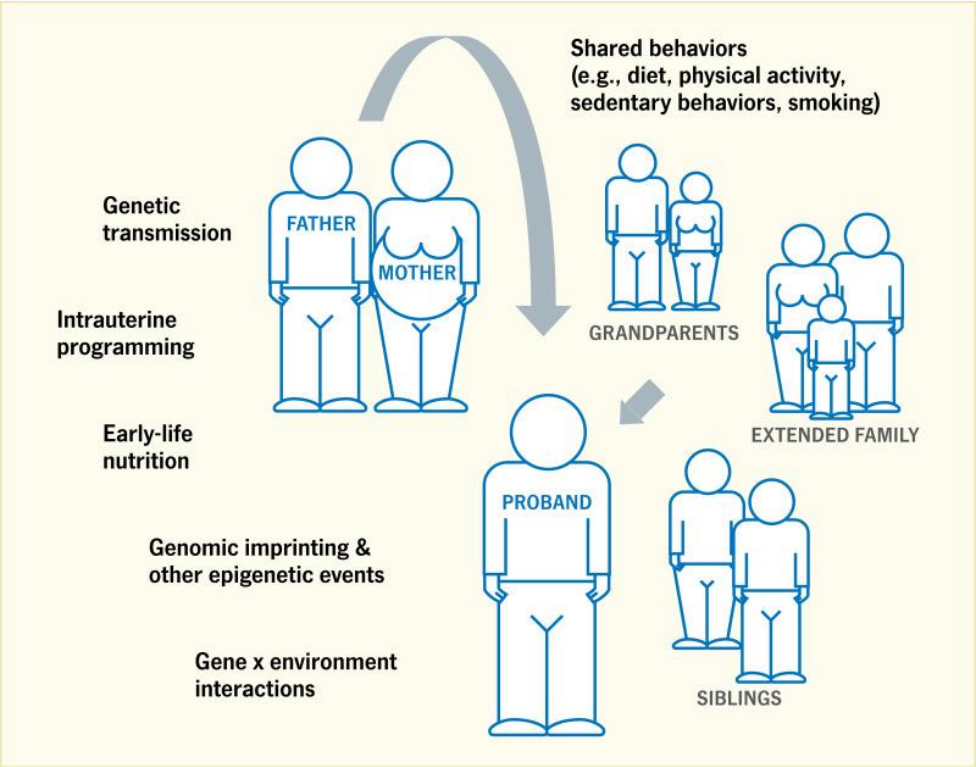

Figure 22 : *Diabetes Risk in the Proband and the Complex Interplay Between Genes, Shared Environment, Shared Behaviors, and Epigenetic Effects*[120]

II.3.1.3. Ethnicity

Ethnicity significantly influences type 2 diabetes mellitus (T2DM) risk, with higher prevalence among non-Hispanic blacks (12.6%), Hispanics/Latinos (11.8%), and Asian Americans (8.4%) compared to non-Hispanic whites (7.1%) in the U.S., with total prevalence (diagnosed and undiagnosed) twice as high in Asian Americans . Ethnic disparities persist partially independent of obesity, behavioral factors, and socioeconomic status, though socioeconomic adjustments attenuate risk in non-Hispanic black women but not men . Studies, including the Nurses' Health Study and Multiethnic Cohort Study, confirm elevated T2DM risk in Asian, Hispanic, black, Japanese American, and Pacific Islander populations compared to whites, even after adjusting for BMI, family history, and lifestyle factors, suggesting genetic, migration, and acculturation influences[120]

II.3.1.4. History of Gestational Diabetes.

A history of gestational diabetes mellitus (GDM), defined as glucose intolerance first recognized during pregnancy, significantly increases the risk of developing type 2 diabetes mellitus (T2DM) for both the mother and her children. Progression to T2DM is influenced by pre-pregnancy obesity, the need for insulin during pregnancy, and higher glucose levels

during oral glucose tolerance testing . Risk factors for GDM include family history of diabetes, advanced maternal age, nonwhite ethnicity, higher BMI, early adulthood weight gain, and smoking, with ethnicity strongly affecting postpartum T2DM risk, particularly in high-risk groups where obesity and physical inactivity are prevalent[121]

II.3.1.5. Polycystic ovary syndrome (PCOS)

Polycystic ovary syndrome (PCOS) significantly increases type 2 diabetes mellitus (T2DM) risk, with rapid conversion from normal or impaired glucose tolerance to T2DM, often exceeding 15% per year, suggesting earlier onset compared to the general population . Higher baseline BMI, fasting glucose, and glucose response to glycemic load independently predict T2DM, while elevated sex hormone-binding globulin (SHBG) levels at follow-up reduce risk, possibly by modulating free testosterone or reflecting metabolic health . Obesity, prevalent in PCOS, markedly amplifies T2DM risk, especially in obese women, though it's unclear if PCOS confers intrinsic risk beyond obesity[122]

II.3.2. Modifiable Risk Factors:

II.3.2.1. Obesity and Overweight:

Obesity and overweight significantly increase type 2 diabetes mellitus (T2DM) risk through insulin resistance driven by visceral white adipose tissue (WAT) expansion, ectopic fat accumulation, and adipose tissue dysfunction . Visceral WAT, characterized by large adipocytes, promotes lipolysis, releasing free fatty acids (FFAs) that impair insulin signaling via serine phosphorylation of insulin receptor substrates (IRS1/2) and increase hepatic gluconeogenesis, exacerbating hyperglycemia.[123]

Dysfunctional adipogenesis, linked to impaired PPARγ and BMP4 signaling, leads to adipocyte hypertrophy and ectopic lipid storage in muscle and liver, causing mitochondrial dysfunction, reactive oxygen species (ROS) production, and endoplasmic reticulum (ER) stress, which activate proinflammatory cytokines (e.g., TNF-α, IL-6) and NF-κB, further driving insulin resistance . [123]

Brown adipose tissue (BAT) dysfunction reduces thermogenesis, worsening insulin sensitivity, while low adiponectin levels, common in obesity, diminish insulin-sensitizing effects . Adipose tissue inflammation, mediated by macrophage infiltration and adipokines like IL-6 and PAI-1, exacerbates metabolic dysfunction, with dyslipidemia (elevated

triglycerides, reduced HDL) impairing lipoprotein clearance and contributing to T2DM pathogenesis[123]

II.3.2.2. Physical Inactivity

Physical inactivity heightens type 2 diabetes mellitus (T2DM) risk, with sedentary behaviors like excessive television viewing increasing risk independently of BMI[120] . Older age and higher BMI exacerbate sedentary time and low activity levels, worsening prediabetes and T2DM risk [119]. Moderate-intensity activities, such as brisk walking ≥2.5 hours weekly, improve insulin sensitivity and reduce T2DM risk, particularly in high-risk individuals . Lifestyle interventions with 150 minutes of weekly moderate-to-vigorous activity, diet changes, and 5–7% weight loss prevent or delay T2DM, while reducing sedentary time further lowers insulin resistance. [119].

II.3.2.3. Unhealthy Diet:

Unhealthy diets, characterized by high consumption of sugar-sweetened beverages, processed red meat, refined grains, and alcohol, and low intake of fruits, vegetables, fiber, and whole grains, significantly increase type 2 diabetes mellitus (T2DM) risk, even after adjusting for BMI[119].

High glycemic index (GI) and glycemic load (GL) diets elevate T2DM risk by inducing excessive insulin secretion or β-cell toxicity, while diets rich in trans fats and heme iron from red meat promote oxidative stress and impair glucose metabolism . Conversely, diets high in polyunsaturated fats, cereal fiber, magnesium, zinc, and anthocyanins (e.g., from blueberries) reduce T2DM risk[124].

Adherence to Mediterranean, DASH, or AHEI dietary patterns, emphasizing plant-based foods, olive oil, and low processed meat intake, lowers T2DM risk, with Mediterranean diets showing consistent benefits in trials . Western dietary patterns, high in processed foods and sweets, increase T2DM risk by 19–49%, while skipping breakfast or irregular meal patterns further elevates risk[124]

II.3.2.4. Hypertension:

Hypertension and prehypertension significantly increase the risk of type 2 diabetes mellitus (T2DM) in adults, with higher blood pressure (BP) linked to elevated T2DM risk independent of major diabetes risk factors . Prehypertension and hypertension raise T2DM risk by 32% and 102%, respectively, with an 8% increased risk per 10 mm Hg rise in systolic

BP or 6% per 5 mm Hg in diastolic BP . Stronger associations are observed in adults under 50 and those with normal glucose tolerance, suggesting BP's role diminishes with prediabetes [125]

II.3.2.5. Dyslipidemia:

Dyslipidemia, characterized by high triglycerides, low HDL cholesterol, and small dense LDL particles, significantly increases type 2 diabetes mellitus (T2DM) risk and precedes hyperglycemia, often within metabolic syndrome alongside obesity and insulin resistance.[126]

Insulin resistance or deficiency activates hormone-sensitive lipase, elevating non-esterified fatty acids (NEFAs), which boost hepatic triglyceride and apolipoprotein B production, leading to triglyceride-rich VLDL and reduced lipoprotein lipase activity, exacerbating hypertriglyceridemia and postprandial lipemia [38]. This promotes atherogenic small dense LDL and lowers HDL cholesterol via cholesteryl ester transfer, accelerating atherosclerosis before T2DM diagnosis. [126]

Low HDL cholesterol independently predicts T2DM development, while glycated LDL and dysfunctional HDL impair insulin signaling and β-cell protection, further driving T2DM risk. [126]

II.3.2.6. Smoking:

Smoking significantly increases type 2 diabetes mellitus (T2DM) risk, with active smokers exhibiting a dose-dependent risk elevation, particularly heavier smokers, while former smokers and those exposed to passive smoke also face increased risk [120]. Nicotine, a key cigarette component, worsens insulin resistance, promotes lipolysis, and impairs β-cell function via oxidative stress and inflammatory pathways, including increased IRS-1 Ser636 phosphorylation and reduced PPAR-γ expression in skeletal muscle[127]

Smoking alters body composition, increasing visceral fat and waist-to-hip ratios, further exacerbating insulin resistance. Epigenetic changes, such as altered DNA methylation in insulin signaling genes, may contribute to T2DM susceptibility . Smoking during pregnancy raises gestational diabetes risk and offspring T2DM risk, linked to impaired β-cell function . Smoking cessation may initially increase T2DM risk due to weight gain, but short-term cessation improves insulin sensitivity, highlighting the importance of

cessation strategies, though nicotine replacement therapies require further study for long-term glucose homeostasis effects[127]

II.3.2.7. Sleep Deprivation and Poor Sleep Quality:

Sleep deprivation and poor sleep quality significantly elevate type 2 diabetes mellitus (T2DM) risk, with short sleep (≤5–6 hours/night) and long sleep (>8–9 hours/night) both linked to increased risk, as are difficulties initiating or maintaining sleep Shift work, disrupting circadian rhythms, further heightens T2DM risk through endocrinologic imbalances . Mechanisms include reduced glucose tolerance and insulin sensitivity, elevated evening cortisol, increased ghrelin, reduced leptin, and heightened hunger, promoting food intake and reduced energy expenditure, leading to insulin resistance . Long sleep duration may reflect psychiatric comorbidities like depression, increasing sleep fragmentation and reducing daytime activity, thus contributing to T2DM risk[120]

II.4. Clinical Manifestations and Complications of Type 2 Diabetes Mellitus

II.4.1. Classic Symptoms (Often Subtle in Early Stages):

T2DM symptoms often subtle or absent early, developing gradually, delaying diagnosis [43].

Hyperglycemic symptoms:

- excessive thirst
- frequent urination
- Fatigue
- weight loss
- blurred vision,
- trouble concentrating,
- nausea,
- dizziness,
- genital itching,
- stomatitis,

- balanitis [128]

T2DM-specific symptoms:

- tingling,
- pain,
- numbness in extremities[129]

Additional symptoms:

- frequent infections,
- slow-healing sores,
- erectile dysfunction [130]

Symptoms typically short-duration pre-diagnosis, strongly tied to glycemic levels, less to BMI or blood pressure[128]

General practitioners act on hyperglycemic symptoms, but cardiovascular risk-based screening recommended for earlier detection[128]

II.4.2. Acute Complications (Less Common in T2DM at Onset):

- Hyperosmolar Hyperglycemic State (HHS).

Hyperosmolar hyperglycemic state (HHS), a severe acute complication of type 2 diabetes mellitus (T2DM), presents with extreme hyperglycemia (>600 mg/dL), hyperosmolality (>320 mmol/kg), and profound dehydration, primarily in elderly patients, triggered by infections, cardiovascular events, or medication non-adherence . Unlike diabetic ketoacidosis, HHS features minimal ketosis due to sufficient insulin levels preventing ketone production, despite relative insulin deficiency and elevated counterregulatory hormones like cortisol and glucagon, which drive osmotic diuresis and dehydration[131]

Symptoms, including polyuria, polydipsia, weight loss, and severe mental status changes from stupor to coma, develop gradually over days. [131]

Diagnosis requires serum glucose >600 mg/dL, osmolality >320 mmol/kg, and pH >7.30, with elevated blood urea nitrogen indicating mortality risk. [131]

Treatment involves aggressive rehydration, insulin therapy, electrolyte correction, and management of underlying triggers, though HHS carries a high mortality rate of 15%, with overlap cases involving DKA showing elevated mortality[131]

II.4.3. Chronic Microvascular Complications :

Chronic microvascular complications of type 2 diabetes mellitus (T2DM) include diabetic retinopathy, nephropathy, and neuropathy, significantly impacting patient health.

Diabetic retinopathy, a leading cause of blindness in the Western world, results from chronic hyperglycemia-induced microvascular damage to retinal vessels, causing edema and hemorrhage into the retina or vitreous humor, often evident at diagnosis due to prior dysglycemia [132]

Diabetic nephropathy, characterized by microalbuminuria undetectable by routine urinalysis, progresses to renal insufficiency if not identified early through specific testing, which is often overlooked due to lack of awareness[132]

Diabetic neuropathy leads to sensory disturbances, muscle atrophy, and intense lower extremity pain, contributing to foot ulcers, non-healing wounds, infections (e.g., cellulitis, osteomyelitis), and amputations due to loss of protective sensation, alongside autonomic symptoms like tachycardia, orthostatic hypotension, urinary incontinence, and gastrointestinal issues[133]

. Sexual dysfunction in younger patients arises from oxidative stress in cavernous tissues[132]

II.4.4. Chronic Macrovascular Complications:

Cardiovascular Disease (CVD):

Cardiovascular disease (CVD) represents a primary cause of mortality and morbidity in both prediabetes and type 2 diabetes mellitus (T2DM), driven by oxidative stress that promotes atherogenesis and low-density lipoprotein (LDL) oxidation . This oxidative process accelerates the development of atherosclerosis, increasing the risk of premature cardiovascular events . Effective prevention strategies involve a multifaceted approach, including the use of antihypertensive medications, lipid-lowering agents, and routine low-dose aspirin administration to mitigate cardiovascular risk and improve outcomes in T2DM patients [132]

II.5. Management of Type 2 Diabetes Mellitus

II.5.1. Lifestyle Modifications

Physical Activity

Regular physical activity is critical for managing type 2 diabetes mellitus (T2DM), improving glycemic control through increased glucose uptake by active muscles, enhanced insulin sensitivity, and reduced fasting blood glucose for up to 24 hours post-exercise . Moderate daily activities like walking, gardening, or household chores, particularly walking, effectively control long-term T2DM complications with minimal physical strain, while aerobic exercise improves HbA1c, mitochondrial density, vascular compliance, and cardiac output[134]

Reducing sedentary behavior is equally vital, as prolonged inactivity correlates with uncontrolled glycemic levels; increasing physical work enhances energy expenditure and mitigates this risk. [134] The Finnish Diabetes Prevention Study demonstrated that 30 minutes of daily moderate-intensity exercise, combined with dietary changes, reduced T2DM incidence by 58% over four years, with more vigorous leisure-time activity further lowering risk[135]

Dietary Changes and Medical Nutrition Therapy

Dietary modifications are essential for T2DM management, with high intake of sugars, fried foods, and red meat linked to insulin resistance, while antioxidant- and fiber-rich vegetables reduce T2DM risk . Caloric intake should be tailored to obesity status—1,500–2,500 calories/day for nonobese and 800–1,500 for obese patients—with limited refined sugars, replaced by non-nutritive sweeteners, and reduced saturated fats substituted with polyunsaturated fats . Smaller, frequent meals prevent postprandial glucose spikes, and Paleolithic diets rich in lean meats, fish, fruits, and vegetables improve glucose handling[134]

Medical nutrition therapy, delivered by registered dieticians, enhances clinical outcomes, reducing reliance on oral hypoglycemic agents through evidence-based nutrition care[134]. Flexible macronutrient distribution (e.g., 46% carbohydrates, 32–34% fats) achieves similar improvements in HbA1c and LDL cholesterol, while protein intake (10–20% of calories) should be restricted to 0.8 g/kg in nephropathy to prevent progression, prioritizing vegetable over animal proteins[136]

II.5.2. Pharmacological Interventions

ORAL HYPOGLYCAEMIC AGENTS

Several oral hypoglycaemic agents have been widely used for managing type 2 diabetes for many years. Additionally, recent additions to the market promise alternative treatments that will be available shortly.[137]

Table 2 : *Oral hypoglycaemic agents*

Class of drug	Name	Indications for use and cautions
Biguanide	Metformin	First line of therapy in overweight people. May cause diarrhoea, and so should be introduced gradually
Sulphonylureas	Chlorpropamide Tolbutamide Glibenclamide Gliclazide Glipizide Gliquidone Glimepiride	Augment insulin secretion from the beta cells; may also enhance insulin sensitivity. May cause weight gain and hypoglycaemia
Alpha-glucosidase inhibitor	Acarbose	Delays absorption of carbohydrate, reducing postprandial blood glucose levels. May cause excessive flatulence — potentially avoided by gradual introduction
Insulin secretatogue	Repaglinide	Increases insulin production in the presence of hyperglycaemia, thus reducing postprandial blood glucose. Short mode of action, less likely to cause hypoglycaemia than sulphonylureas
Thiazolidinediones	Rosiglitazone Pioglitazone	Likely to be available soon. Increase insulin sensitivity, thereby combating insulin resistance and preserving beta cell function

INSULIN THERAPY IN TYPE 2 DIABETES

Insulin therapy is increasingly being used in type 2 diabetes to either supplement or replace oral therapy. Achieving good glycaemic control by any means is key to preventing long-term complications. In light of this information, insulin should no longer be seen as a last resort to be avoided whenever possible, but rather as an appropriate treatment choice when adequate glycaemic control is not achieved through diet, exercise, and oral medication. Side effects of insulin therapy include weight gain and hypoglycaemia, both of which can

be minimized through careful titration of the insulin dose and attention to relevant lifestyle issues. In patients who are overweight, substantial doses of insulin may be required to overcome their insulin resistance. [137]

Monitoring and Self-Management:

Self-management in type 2 diabetes mellitus (T2DM) goes beyond controlling blood sugar levels; it includes cognitive, practical, and social skills tailored to each person's life context . Patients create individualized strategies that range from organized daily routines to nuanced situational adjustments, although adherence can fluctuate, with some days seeing high compliance and others not as much . Cognitive skills are about adapting management plans through reasoning, practical skills focus on daily tasks such as blood glucose monitoring, and social skills involve reaching out for assistance from diabetes specialist nurses (DSNs) and family caregivers, which greatly improves self-management[138]

II.5.3. Goals of Diabetes Management

Minimizing Complications

Type 2 diabetes mellitus (T2DM) management prioritizes reducing cardiovascular risks through tailored lifestyle changes, addressing smoking, alcohol, stress, and poor foot/dental care to prevent strokes and heart attacks

Tailored Nutrition

Customized diets, based on body composition and activity level, emphasize balanced food groups while limiting low-nutrient foods to optimize glycemic control

Promoting Exercise

Aerobic and strength exercises improve blood sugar, insulin sensitivity, and cardiovascular health, with gradual routines to ensure safety and adherence

Stress Management

Coping strategies like mindfulness and short workouts help maintain healthy routines during stress, supporting metabolic control

Gradual Goals

Small, trackable lifestyle changes, such as adjusting meals or exercise, ensure sustainable T2DM management

Regular Monitoring

Frequent check-ups monitor key health metrics, with group classes offering education and peer support to enhance adherence[139]

Part II: Chapter 03

II.1. The Impact of Type 2 Diabetes on Sarcopenia (Diabetic Sarcopenia)

II.1.1. Accelerated Muscle Loss in Individuals with T2DM:

II.1.1.1. Epidemiology and Prevalence

Type 2 diabetes mellitus (T2DM) is associated with an elevated prevalence and accelerated progression of sarcopenia. Studies indicate a higher prevalence of sarcopenia in T2DM patients compared to age-matched controls, with rates varying by diagnostic criteria. Using the European Working Group on Sarcopenia in Older People (EWGSOP) 2010 criteria, prevalence in T2DM patients was 16.9%, while the 2018 criteria reported 7%.

The Asian Working Group for Sarcopenia (AWGS) criteria identified 58% of elderly T2DM patients with pre-sarcopenia or sarcopenia, including 24% with sarcopenia and 4% with severe sarcopenia . Rapid declines in appendicular lean mass, indicative of skeletal muscle mass, occur in older adults with T2DM, independent of weight changes.[140]

II.1.1.2. Sex Differences in Muscle Loss

A significant sex-diabetes interaction affects muscle mass loss. Older women with T2DM experience accelerated thigh muscle loss compared to non-diabetic women, negating the protective effect of female sex on muscle preservation.[141]

In contrast, men without T2DM exhibit higher baseline muscle mass declines, which may obscure additional T2DM-related changes. Women with T2DM lose thigh muscle mass at rates comparable to non-diabetic men. These findings align with observations that muscle mass declines are generally greater in men than women, though T2DM amplifies loss in women.[141]

II.1.1.3. Pathological Changes in Muscle Fibers

T2DM-related sarcopenia exhibits distinct muscle fiber changes compared to age-related sarcopenia. While sarcopenia primarily involves type II (fast-twitch) fiber atrophy , T2DM-related sarcopenia is characterized by a reduction in type I fibers and an increase in type II fibers, particularly type IIx or IIb. [140]

Studies show a lower proportion of type I fibers in T2DM patients compared to healthy or obese controls, with increased type IIb or IIx fibers. This shift is associated with reduced oxidative enzyme activity and lower glucose transporter 4 (GLUT4) density in slow-twitch fibers, suggesting impaired glucose uptake due to disrupted insulin signaling. These changes may reflect a compensatory mechanism to maintain rapid muscle contractions amid insulin

resistance. T2DM patients also exhibit higher intramyocellular lipid content and reduced mitochondrial respiratory activity, impacting muscle metabolism[140]

II.1.1.4. Impact on Endocrine and Metabolic Regulation

Sarcopenia in T2DM patients adversely affects endocrine metabolism. T2DM patients with sarcopenia show higher glycated hemoglobin (HbA1c) levels, poorer nutritional status, imbalanced nutrient intake, deteriorating glucose metabolism, declining kidney function, and increased osteoporosis risk compared to non-sarcopenic diabetic controls. The reduction in type I fibers, critical for aerobic metabolism, impairs energy utilization, affecting metabolic health[140]

II.1.2. Underlying Mechanisms Contributing to Diabetic Sarcopenia:

II.1.2.1. Insulin Resistance and Impaired Muscle Protein Metabolism:

Insulin resistance (IR) is a hallmark of type 2 diabetes mellitus (T2DM) and a primary mechanism driving sarcopenia by disrupting skeletal muscle protein metabolism. Impaired insulin action in skeletal muscle promotes protein degradation and hampers protein synthesis, leading to reductions in muscle mass and strength. IR is a critical factor exacerbating sarcopenia in T2DM patients,

II.1.2.1.1. Dysregulated Protein Synthesis and Degradation Pathways

Muscle protein synthesis is primarily regulated by the insulin-like growth factor 1 (IGF-1) and PI3K/Akt/mTOR signaling pathways, while protein degradation involves multiple pathways, including the ATP-dependent ubiquitin-proteasome pathway (UPP), lysosomal autophagy, caspase hydrolysis, and calcium-dependent calpain pathways. These pathways are mediated by signaling molecules such as IL-6/STAT, TNF-α/IL-6/NFκB, myostatin/Smad2/3, and FoxO1/3. In T2DM, IR inhibits the mammalian target of rapamycin complex 1 (mTORC1), reducing protein synthesis, while simultaneously stimulating the UPP through FoxO family proteins and downstream E3 ubiquitin ligases (e.g., Atrogin-1, MuRF1), increasing protein catabolism. Insulin typically reduces proteasome catalytic activity, but IR disrupts this process, leading to muscle atrophy via the UPP. Additionally, IR increases FoxO1 expression, which inhibits mTORC1 and induces autophagy, further contributing to muscle loss. The interaction between IL-6 and IGF-1 pathways can modulate

inflammatory responses, potentially alleviating sarcopenia, but this requires further exploration[142]

II.1.2.1.2. Role of Hyperglycemia and Glycemic Control

Hyperglycemia resulting from IR exacerbates muscle atrophy through the WWP1/KLF15 pathway. In diabetic animal models, hyperglycemia upregulates KLF15, a protein associated with muscle wasting, by downregulating the E3 ubiquitin ligase WWP1, inhibiting ubiquitin-dependent degradation of KLF15. This leads to increased expression of muscle atrophy-related genes. Mice with muscle-specific KLF15 deficiency are protected from diabetes-induced muscle atrophy, suggesting this pathway as a potential therapeutic target. Poor glycemic control, indicated by glycated hemoglobin (HbA1c) levels ≥8.5%, is associated with reduced lower-limb muscle quality and physical performance in older T2DM patients. Knee extensor strength decreases across increasing HbA1c quartiles, reflecting impaired protein metabolism due to increased protein degradation and decreased synthesis, particularly in undiagnosed T2DM patients with greater glucose variability[143]

II.1.2.2. Chronic Low-Grade Inflammation and Advanced Glycation End Products (AGEs):

Chronic low-grade inflammation in type 2 diabetes mellitus (T2DM) drives sarcopenia by disrupting muscle and glucose homeostasis. Elevated pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and C-reactive protein (CRP), are associated with insulin resistance and adiposity, reducing muscle mass, strength, and performance[143]

II.1.2.2.1. Pro-Inflammatory Cytokines

Visceral adipose tissue secretes IL-6 and TNF-α, activating JNK, NF-κB, and STAT3 pathways, which impair insulin signaling and reduce GLUT4 expression, causing insulin resistance. IL-6 promotes muscle catabolism when chronically elevated but supports muscle hypertrophy when produced by myocytes during exercise. Higher IL-6 and IL-6/IL-10 ratios correlate with sarcopenia, and T2DM patients show greater muscle loss, partially linked to IL-6 and TNF-α[144]

II.1.2.2.2. Anti-Inflammatory Cytokines

IL-10 suppresses IL-6 and TNF-α, enhancing insulin sensitivity and myogenesis. Low IL-10 levels in obese T2DM patients contribute to insulin resistance and muscle loss, though IL-10 may also induce mitophagy, potentially promoting atrophy[145]

II.1.2.2.3. Protein Degradation

Inflammation downregulates protein synthesis via the PI3K-Akt pathway and upregulates protein catabolism through the ubiquitin-proteasome system (UPS) and autophagy. NF-κB and STAT3 increase MuRF1 expression, while IL-6-activated STAT3 inhibits protein synthesis via SOCS3 and myostatin. Chronic IL-6 impairs satellite cell function, and hyperglycemia activates apoptosis pathways, worsening muscle loss[145]

II.1.2.2.4. mTORC1 Dysregulation

Chronic hyperglycemia overactivates mTORC1, impairing insulin signaling and causing muscle fiber damage. mTORC1 inhibitors, like rapalog, improve muscle mass, suggesting a therapeutic target[144]

II.1.2.2.5. Muscle Mass and Strength Impact

Higher IL-6 and CRP levels predict greater lean mass loss, particularly in women, and reduced handgrip strength. T2DM patients lose more leg muscle mass and strength over time, driven by inflammation[143]

II.1.2.2.6. Advanced Glycation End-Products (AGEs)

AGEs, heterogeneous molecules formed by non-enzymatic reactions between glucose and proteins, lipids, or nucleic acids, accumulate in T2DM due to chronic hyperglycemia and are positively associated with insulin resistance, obesity, and aging. AGEs contribute to skeletal muscle atrophy and dysfunction by affecting biomechanical properties of neuromusculoskeletal tissues, including muscle, bone, cartilage, tendons, ligaments, and nerves. AGEs interfere with muscle contractility through increased protein cross-linking and charge changes, impairing muscle function. By binding to AGE receptors (RAGE) on skeletal muscle cell membranes, AGEs induce inflammation, activate NADPH oxidase, and increase reactive oxygen species (ROS), promoting oxidative stress and mitochondrial dysfunction, which lead to cell death and muscle atrophy[143]

II.1.2.3. Oxidative Stress in Diabetic Muscle:

Oxidative stress, characterized by excessive reactive oxygen species (ROS) and reduced antioxidant capacity, is a key contributor to sarcopenia in type 2 diabetes mellitus

(T2DM). Driven by hyperglycemia, insulin resistance, mitochondrial dysfunction, and advanced glycation end-products (AGEs), oxidative stress promotes muscle atrophy by impairing protein synthesis and accelerating protein degradation[144]

II.1.2.3.1. Hyperglycemia-Induced ROS and Protein Degradation

Hyperglycemia in T2DM triggers overproduction of ROS, such as superoxide anions, which activate the ubiquitin-proteasome system (UPS). This leads to increased expression of proteasome subunits (C2, C9) and MuRF1, accelerating muscle protein degradation. ROS also activates protein kinase R (PKR), further promoting muscle atrophy. Experimental studies show that high glucose levels reduce protein synthesis and enhance degradation via the UPS, contributing to muscle loss[142]

II.1.2.3.2. Mitochondrial Dysfunction

Mitochondrial dysfunction, exacerbated by T2DM and aging, increases oxidative stress and impairs muscle function. T2DM patients exhibit a 45% lower phosphocreatine recovery half-life post-exercise, indicating reduced mitochondrial function, while first-degree relatives show 38% lower mitochondrial density. In the elderly, oxidative capacity per muscle unit is reduced by 50%, accompanied by mitochondrial DNA mutations. Diabetes-induced mitochondrial dysfunction causes myocyte apoptosis, increasing sarcopenia risk[144]

II.1.2.3.3. Impaired Muscle Repair and Signaling Pathways

Oxidative stress inhibits muscle repair by impairing satellite cell differentiation and DNA integrity in diabetic models. It suppresses the Akt/mTOR pathway, reducing protein synthesis, and activates calpains, non-lysosomal Ca^{2+}-regulated enzymes, which promote muscle atrophy by inhibiting Akt and activating the UPS. Loss of Ca^{2+} homeostasis in T2DM further exacerbates calpain activity[142]

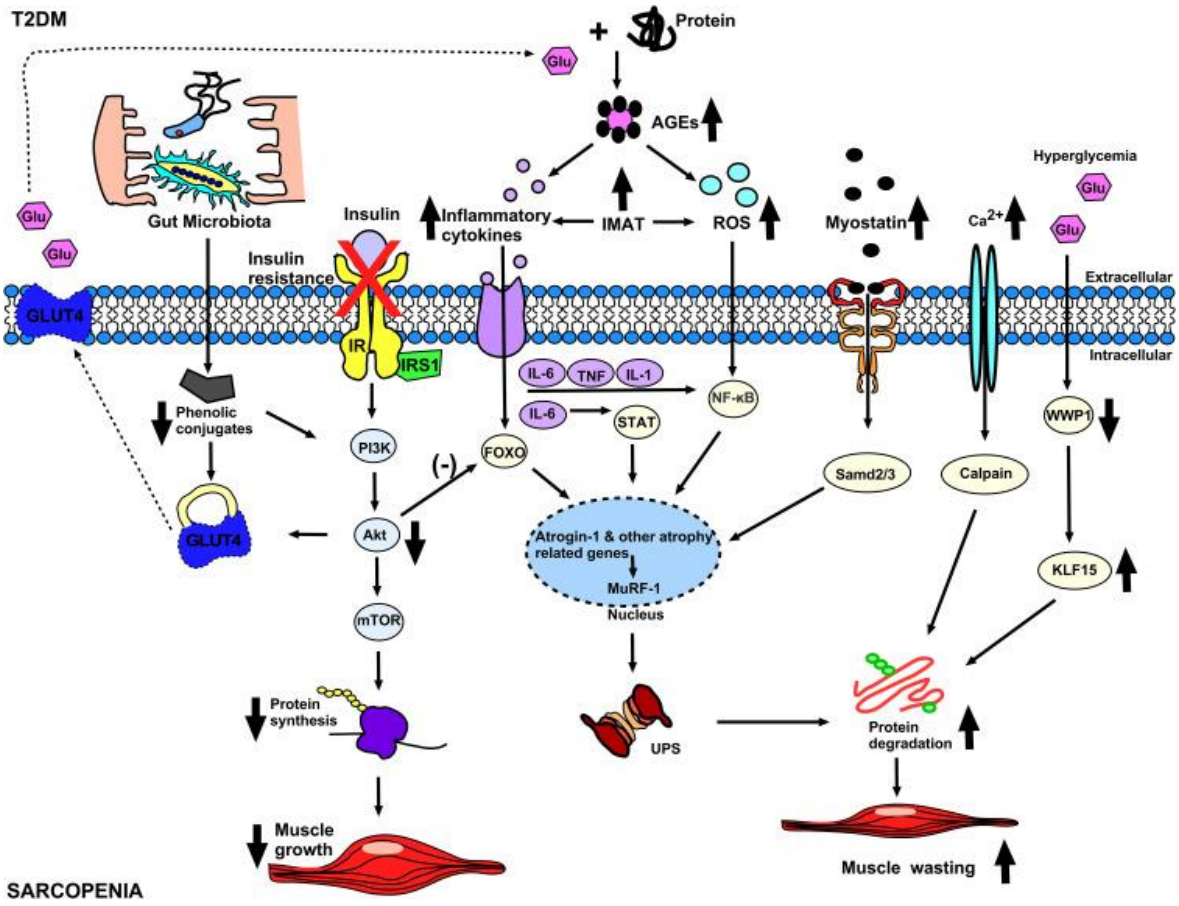

Figure 23 : *The possible mechanism of diabetes and sarcopenia*[143]

II.1.2.4. Microvascular Complications and Impaired Muscle Perfusion:

Microvascular complications of type 2 diabetes mellitus (T2DM), including diabetic nephropathy, neuropathy, and retinopathy, contribute to sarcopenia by impairing muscle perfusion, reducing strength, and promoting atrophy. These complications disrupt blood supply to muscles and nerves, driving inflammation and metabolic dysregulation that accelerate muscle loss[144]

II.1.2.4.1. Diabetic Nephropathy

Diabetic nephropathy (DKD), affecting 24.4%–40% of T2DM patients, is linked to sarcopenia through bidirectional mechanisms. Chronic hyperglycemia causes kidney damage, while chronic kidney disease (CKD) promotes muscle loss via inflammation, insulin resistance, and reduced protein synthesis. Sarcopenia increases albuminuria risk , and DKD is associated with a 2.5-fold higher sarcopenia odds. Lower glomerular filtration rate

(eGFR) and higher C-reactive protein correlate with reduced muscle mass, and CKD patients show decreased mitochondrial volume, exacerbating muscle wasting[143]

II.1.2.4.2. Diabetic Neuropathy

Diabetic neuropathy, prevalent in up to 61.8% of T2DM patients, accelerates sarcopenia by damaging nerve capillaries, causing muscle weakness and atrophy. T2DM patients with neuropathy have lower knee extension strength and poorer physical performance (e.g., gait speed, balance). Neuropathy is more common in sarcopenic T2DM patients (80% vs. 70.3%), with symptom scores linked to sarcopenia . Neuropathy impairs muscle contractility, contributing to functional decline[144]

II.1.2.4.3. Diabetic Retinopathy

Diabetic retinopathy, affecting ~27% of T2DM patients, indirectly promotes sarcopenia by impairing vision, increasing falls risk , and limiting mobility.

Mobility restrictions from retinopathy exacerbate physical inactivity, driving muscle loss[144]

II.1.2.4.4. Pathophysiological Mechanisms

Microvascular damage impairs muscle perfusion, reducing oxygen and nutrient delivery. Neuropathy disrupts nerve innervation, nephropathy amplifies inflammation and mitochondrial dysfunction, and retinopathy limits activity. Shared pathways, including insulin resistance, inflammation, and AGEs, worsen muscle dysfunction. Sarcopenia may also exacerbate these complications[143]

II.2. The Impact of Sarcopenia on Type 2 Diabetes (Sarcopenia as a Risk Factor and Contributing Factor)

II.2.1. Sarcopenia as a Risk Factor for Developing T2DM:

A 7-year longitudinal study of 3,707 older Chinese adults demonstrated that possible sarcopenia, defined by AWGS 2019 criteria (impaired physical performance and muscle strength), was associated with a 27% increased risk of new-onset T2DM (17.3% incidence in sarcopenic vs. 14% in non-sarcopenic individuals), independent of confounders such as sex, age, BMI, central obesity, residence, smoking/drinking status, fasting glucose, and chronic conditions (e.g., hypertension, hyperlipidemia)[146]

This association was significant in individuals under 75 years and with BMI <24 kg/m², but not in older or higher-BMI groups, suggesting population-specific risk profiles . Longitudinal evidence outperformed prior cross-sectional studies, confirming sarcopenia's predictive role for T2DM[146]

Mechanisms may include reduced muscle mass impairing glucose disposal (accounting for ~80% of postprandial glucose metabolism), sarcopenia-induced insulin resistance, and contributions from oxidative stress, inflammation, and physical inactivity. Metabolic abnormalities (e.g., hypertension, hyperlipidemia) prevalent in sarcopenic individuals further elevate T2DM risk[146]

II.2.2. Mechanisms by Which Sarcopenia Contributes to Insulin Resistance and Metabolic Dysfunction:

Sarcopenia, including its obesity-associated form (SO), contributes to insulin resistance (IR) and metabolic dysfunction, exacerbating type 2 diabetes mellitus (T2DM) progression

II.2.2.1. Reduced Glucose Disposal:

Skeletal muscle is the primary site for insulin-stimulated glucose uptake, and sarcopenia's reduced muscle mass decreases overall glucose disposal capacity. Insulin resistance (IR) impairs the translocation of GLUT4 glucose transporters to the myocyte cell surface, reducing glucose uptake and utilization in skeletal muscle . The resulting loss of muscle mass further exacerbates this impairment, leading to reduced glucose disposal, lowered muscle mass, and diminished strength, all of which contribute to the progression of type 2 diabetes mellitus (T2DM)[147]

II.2.2.2. Altered Adipokine Profile:

Sarcopenia, often associated with sarcopenic obesity (SO), is linked to increased adiposity, which alters the secretion profile of adipokines and contributes to insulin resistance (IR) and systemic inflammation in type 2 diabetes mellitus (T2DM) . The infiltration of skeletal muscle by ectopic fat and intramuscular adipose tissue (IMAT) exacerbates this effect, as IMAT's proximity to muscle may interfere with insulin sensitivity and metabolic function . IMAT secretes proteins that modify the muscle extracellular matrix, potentially influencing insulin sensitivity, and its triglyceride lipolysis increases free fatty acid concentrations, leading to muscle lipid accumulation and IR [148]

Additionally, IMAT exhibits elevated secretion of inflammatory cytokines (e.g., IL-2, IL-18, IL-27, FGF23, CSF1) and some adipokines, alongside anti-inflammatory cytokines (e.g., IL-10, IL-13), suggesting a complex role in local muscle inflammation . This increased infiltration of pro-inflammatory molecules may alter myocyte insulin sensitivity, contributing to metabolic dysfunction . Together, these changes amplify the metabolic risk associated with impaired muscle health, driving T2DM progression[148]

II.2.2.3. Lipid Infiltration and Lipotoxicity in Skeletal Muscle

Sarcopenia promotes abnormal lipid distribution and infiltration (myosteatosis) in skeletal muscle, a hallmark of SO, leading to IR through multiple pathways [28]. Intramuscular lipids (IMCLs) accumulate as lipid droplets (LDs), stabilized by periphospholipid proteins (e.g., PLIN2), with excessive deposition driving lipotoxicity . Key lipid intermediates include:

Diacylglycerol (DAG): 1,2-DAG accumulation activates protein kinase C (PKCθ), inhibiting insulin receptor substrate-1 (IRS-1) and reducing glucose uptake, contributing to IR . However, DAG's impact varies by localization, with mitochondrial and endoplasmic reticulum (ER) 1,2-DAG linked to enhanced oxidative capacity in athletes, highlighting conflicting evidence

Ceramide (CER): Increased CER, transported by CERT proteins, inhibits Akt phosphorylation via protein phosphatase 2A, reducing insulin sensitivity and impairing mitochondrial respiration

Acylcarnitine (ACC): Incomplete lipid oxidation elevates ACC (e.g., C-10, C-12, palmitoylcarnitine), decreasing Akt phosphorylation and mitochondrial function, further promoting IR

Lipid infiltration also triggers inflammation, activating pro-inflammatory cytokines like TNF-α, MCP-1, and IL-6. These polarize macrophages to the pro-inflammatory M1 phenotype, enhancing IKK and JAK-STAT pathways via SOCS1/3, which impair insulin signaling and exacerbate IR

These lipid-induced disruptions likely contribute to elevated HbA1c, a key T2DM marker, though direct evidence requires further study.[147]

II.2.2.4. Reduced Proportion of Type I Muscle Fibers

Sarcopenia decreases type I muscle fibers, which have higher oxidative capacity, correlating with IR severity . Type I fibers contain more mitochondria and capillaries, supporting lipid oxidation and insulin sensitivity . Their reduction, often linked to decreased AMPK phosphorylation, shifts muscle composition toward type II fibers, impairing metabolic function and exacerbating IR . A hypothesis suggests type II fibers may overstimulate insulin secretion, further reducing systemic insulin sensitivity[147]

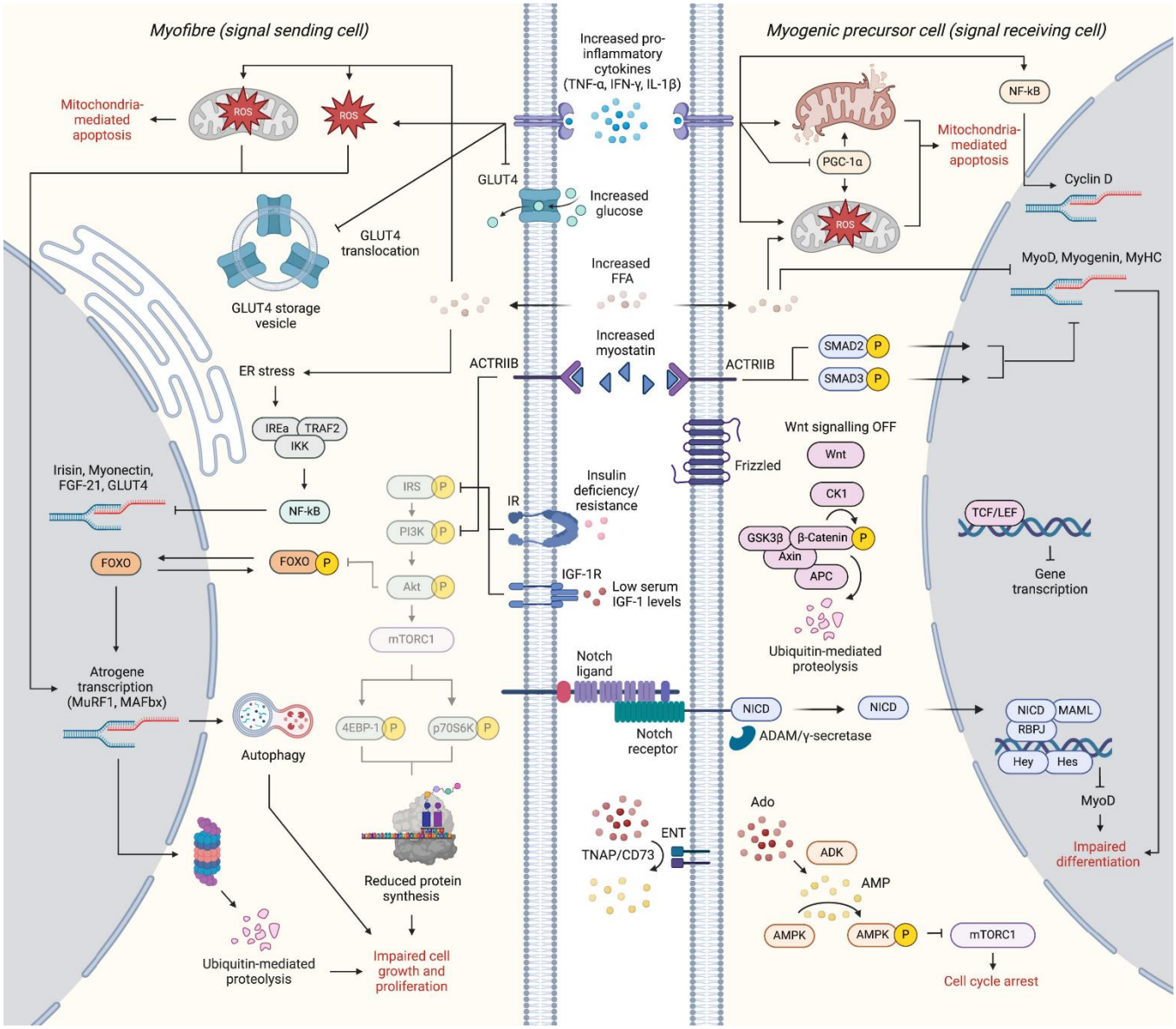

Figure 24 : Mechanisms by which sarcopenia promotes the development and progression of type 2 diabetes mellitus (T2DM) [149]

PART III : MATERIALS AND METHODS

III.3. Research Methodology

III.3.1. Study Domain

The current study investigates the interrelationship between **sarcopenia** (age- and disease-related muscle loss) and **type 2 diabetes mellitus (T2DM)**. Given the emerging scientific evidence of a **bi-directional link** between these two conditions — where T2DM accelerates muscle degradation and sarcopenia impairs glucose metabolism — this study aims to explore how they co-exist in real-world patients and identify potential patterns of association based on demographic, metabolic, and functional variables.

The study is based on **a structured questionnaire** administered to **patients diagnosed with type 2 diabetes**, addressing multiple areas including general health, muscle strength, mobility, diet, awareness of sarcopenia, and perception of its link with diabetes. This empirical approach allows the integration of **epidemiological, functional, and behavioral** data.

III.3.1.1. Temporal Domain

The survey was conducted during the period from **[14 April] to [30 Mai]**. This timeframe was selected to ensure sufficient data collection and to account for seasonal variations in physical activity and lifestyle habits that may influence muscle health.

III.3.1.2. Spatial Domain

The study was conducted in two phases and included participants from various geographical locations.

The first part of the sample (n = 100 participants) was recruited in person from three different healthcare centers in Saida

[1] El-Ogbane Diabetology Center – saida -

[2] Health Center Sidi Sheikh – saida -

[3] Ahmed Medeghri Hospital – saida-

These sites were selected for their high outpatient diabetic population

The second part of the sample consisted of respondents who completed the same structured questionnaire online, distributed via digital platforms. Specifically on Facebook. This group included individuals from across Algeria. The online data collection ensured

broader geographic coverage and included diabetic individuals who may not regularly attend medical institutions.

By combining in-person and online data collection, the study achieved a diverse and representative sample of adults living with type 2 diabetes across multiple settings.

III.3.2. Objective of the Study

The primary objective of this study is to:

Explore the bidirectional relationship between sarcopenia and type 2 diabetes mellitus through clinical, functional, and self-reported data collected from diabetic individuals.

Secondary objectives include:

- Determining the **prevalence of sarcopenia-related symptoms** (e.g., reduced strength, mobility difficulties) in T2DM patients.
- Evaluating the **awareness of sarcopenia** among diabetic individuals.
- Analyzing the **impact of diabetes control (HbA1c levels, disease duration)** on muscle health indicators.
- Investigating the perceived and actual **consequences of sarcopenia on daily life and diabetes management**.

III.3.3. Materials and Methods

III.3.3.1. Study Design

This is a **cross-sectional descriptive study** based on a **quantitative survey** method. Data was collected through a **structured, pre-validated questionnaire** designed to assess the presence of sarcopenic traits and explore the interaction between muscle health and type 2 diabetes.

III.3.3.2. Study Population and Sampling

The study population includes adults aged **≥40 years** who have been clinically diagnosed with **type 2 diabetes mellitus**. Inclusion criteria were:

- Confirmed diagnosis of T2DM.
- Age 40 or older.
- Ability to understand and respond to the questionnaire.

Exclusion criteria included:

- Diagnosis of type 1 diabetes.
- Presence of other neuromuscular or cognitive conditions that impair the ability to answer accurately.

Sampling was **purposive**and involved **[200]** participants.

III.3.3.3. Data Collection Tool

The main tool was a **structured questionnaire** divided into seven sections:

1. **General Information & Health Background**
2. **Muscle Health and Physical Function**
3. **Physical Activity and Lifestyle**
4. **Sarcopenia Awareness and Treatment**
5. **Bidirectional Relationship Between Sarcopenia and T2DM**

The questionnaire included multiple choice, yes/no, Likert-scale, and frequency-based questions to capture a comprehensive profile of each participant.

It was **administered in [Arabic/French/English]**, either in printed form or via in-person interviews.

III.3.4. Data Analysis

Collected data were entered into **Microsoft Excel / SPSS** and analyzed using **descriptive statistics** (percentages, means, and standard deviations). The relationships between muscle-related symptoms and diabetes control variables (e.g., HbA1c, disease duration) were examined.

Results were presented in **tables and graphics**, and discussed in relation to existing literature in the next chapter

.

PART IV : RESULTS AND DISCUSSION

III.1. Sarcopenia in Type 2 Diabetes Mellitus: The Interplay of Age, Gender, Comorbidities, Lifestyle Behaviors, and Dietary Factors

Table 3 : Demographic Characteristics: Age and Gender Distribution

Age Group	Male (%)	Female (%)
Under 40	47.4%	52.6%
40–50	47.7%	52.3%
51–60	36.0%	64.0%
61+	66.1%	33.9%

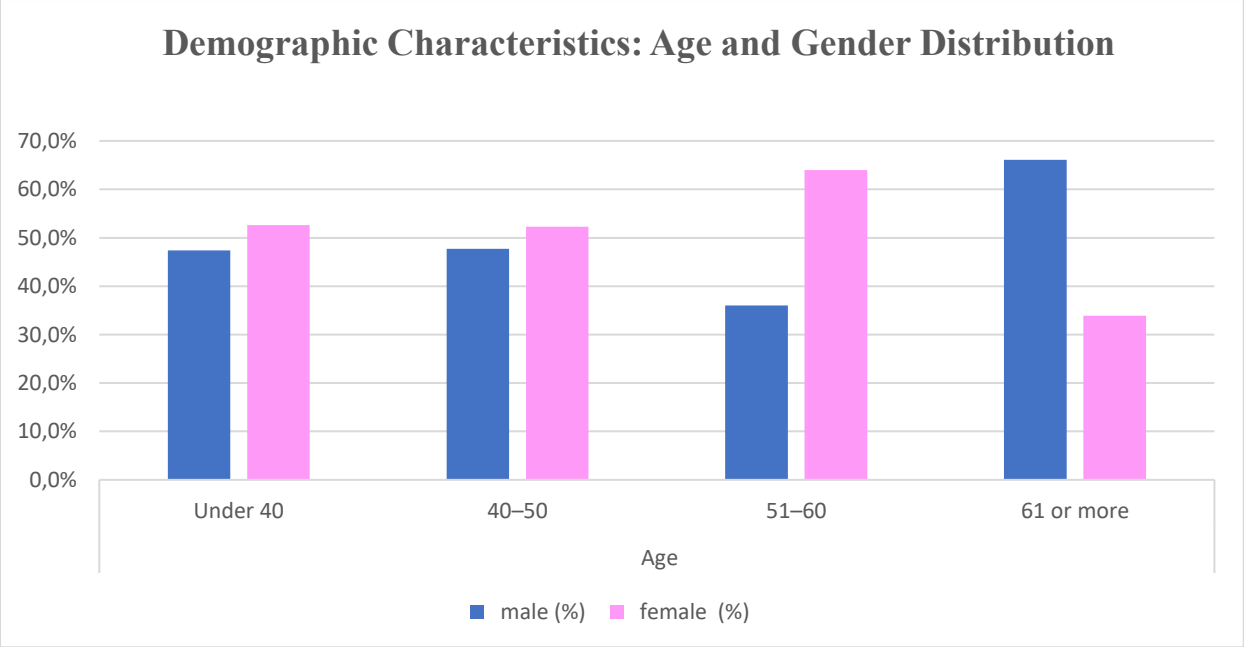

Figure 25 : Demographic Characteristics: Age and Gender Distribution

Table 3 and **figure 25** presents the demographic distribution of 200 individuals with type 2 diabetes mellitus (T2DM), categorized by age and gender. The age groups include under 40, 40–50, 51–60, and 61 years or older. Gender distribution reveals a relatively balanced representation in the younger groups, with a slight female majority in the under 40 (52.6%) and 40–50 (52.3%) brackets. This could reflect higher obesity rates or a history of gestational diabetes, both known risk factors for T2DM in women.

A notable female predominance (64.0%) appears in the 51–60 age group, potentially linked to postmenopausal hormonal changes such as estrogen decline, which is associated with increased insulin resistance and muscle mass loss.

In contrast, males dominate the 61+ group (66.1%), possibly reflecting a combination of longer survival despite complications and age-related testosterone decline, which may impact both glycemic control and muscle health.

These demographic trends underscore the complex interplay between aging, hormonal shifts, and metabolic disorders, supporting the - bidirectional relationship between T2DM and sarcopenia- . As individuals age, changes in sex hormones may contribute to muscle degradation and metabolic dysregulation, reinforcing the need for age- and gender-sensitive interventions.

Table 4 : Protein Intake Among Type 2 Diabetes Patients

Response	Frequency	Percentage
Yes	90	45,0
No	49	24,5
Unsure	61	30,5
Total	200	100,0

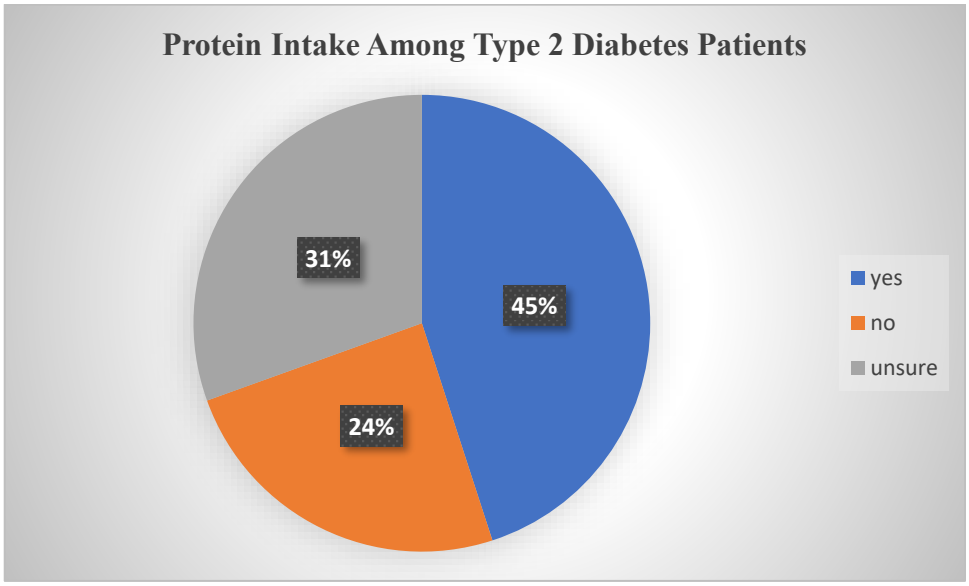

Figure 26 : Protein Intake Among Type 2 Diabetes Patients

Table 04 and **figure 26** investigates perceived protein intake among 200 T2DM patients, with 45.0% feeling their diet includes enough protein-rich foods, 24.5% reporting insufficient intake, and 30.5% unsure.

The 45.0% "Yes" group may benefit from adequate protein, supporting muscle protein synthesis and potentially stabilizing glycemic control by enhancing insulin sensitivity

The 55.0% with insufficient or uncertain intake (24.5% "No" + 30.5% "Unsure") are at risk for sarcopenia due to inadequate muscle support, which could exacerbate T2DM progression through increased insulin resistance This supports a bidirectional T2DM-sarcopenia relationship, where sufficient protein may mitigate muscle loss and improve glucose metabolism, while deficiency or uncertainty may worsen both. The 30.5% uncertainty suggests a need for dietary education

Table 5 : exercise habits by gender among T2DM patients

Gender	**Do you exercise?**		
	Yes	No	Sometimes
Male	41,8%	54,1%	4,1%
female	24,5%	73,5%	2,0%

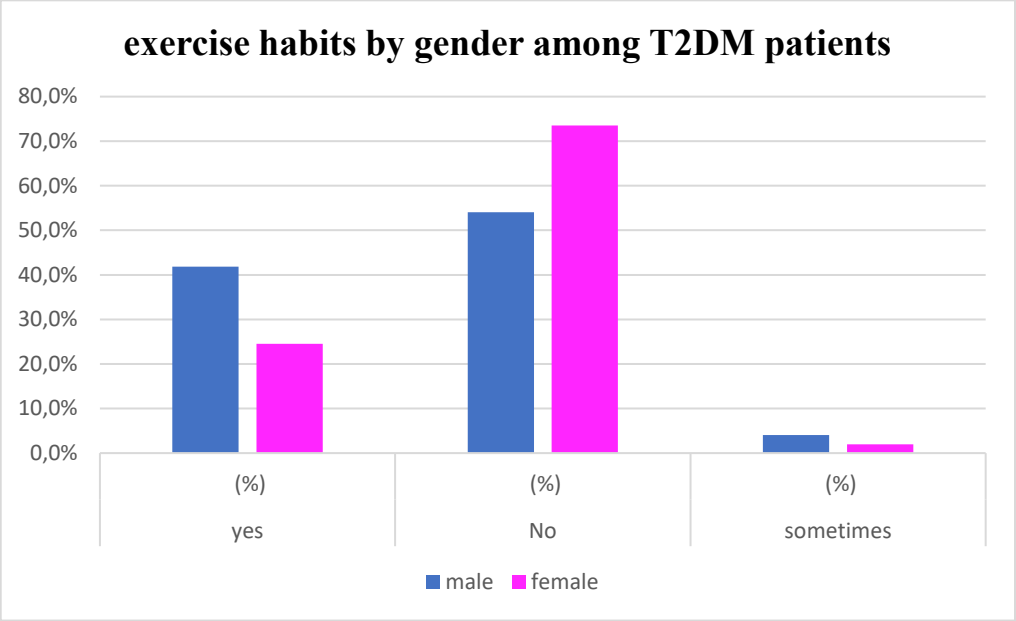

Figure 27 : exercise habits by gender among T2DM patients

Table 05 and **figure 27** examines exercise habits by gender among T2DM patients, with 41.8% of males exercising, 54.1% not exercising, and 4.1% sometimes, compared to 24.5% of females exercising, 73.5% not exercising, and 2.0% sometimes. The 17.3% higher exercise rate among males and the 19.4% higher inactivity rate among females suggest significant gender disparities.

The lower exercise rate among females (24.5% vs. 41.8% for males) starkly manifests gender inequality, particularly pronounced in patriarchal contexts like Arab countries, including Algeria. This disparity is rooted in a culture where women's physical activity is stifled due to ignorance about its health benefits and oppressive control exerted by conservative, strict families. In Algeria, societal norms often prioritize female domestic roles

over personal health, with families restricting daughters from exercising due to concerns about public modesty, safety, or perceived impropriety. The 73.5% female inactivity may increase sarcopenia risk by reducing muscle protein synthesis, while the 41.8% male exercise rate could support muscle preservation and insulin sensitivity.

Table 6 : Prevalence of Comorbidities Among Type 2 Diabetes Patients

health conditions	Frequency	Percentage
High blood pressure	51	25,5
Heart disease	6	3,0
Osteoporosis	7	3,5
Kidney disease	1	0,5
Obesity	31	15,5
None	79	39,5
Other	25	12,5
Total	200	100,0

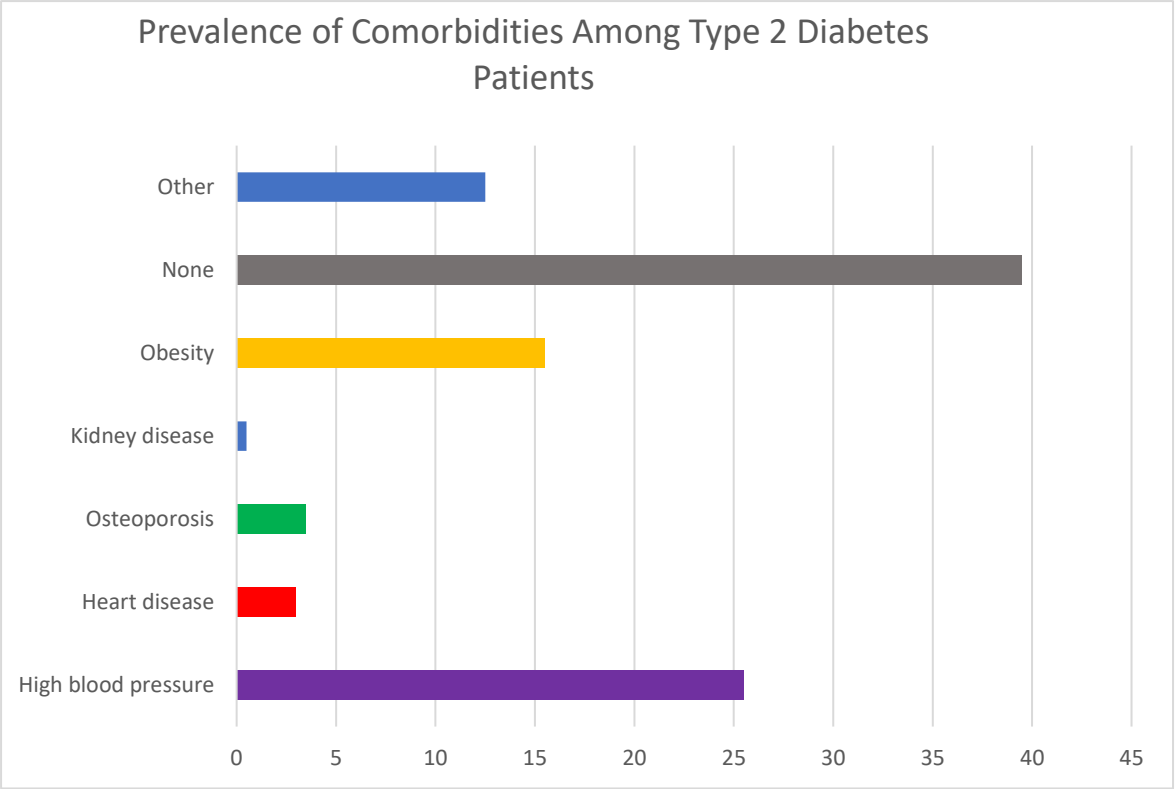

Figure 28 : Prevalence of Comorbidities Among Type 2 Diabetes Patients

Table 6 and **figure 28** details comorbidities in 200 T2DM patients, with 39.5% reporting none, 25.5% high blood pressure, 15.5% obesity, 12.5% other, 3.5% osteoporosis, 3.0% heart disease, and 0.5% kidney disease. The 25.5% with high blood pressure and 15.5% with obesity reflect common T2DM complications, likely exacerbating inflammation and vascular issues that drive the 28.7% significant muscle decline in poorly controlled patients. Osteoporosis (3.5%) suggests a subset with advanced sarcopenia, while the 39.5% with no comorbidities provide a baseline to assess T2DM's independent role,

Table 7 : Age Distribution and Unintentional Weight Loss Among Type 2 Diabetes Patients

Age group	significant decline (%)	slight decline (%)	No change (%)
Under 40	42,1%	47,4%	10,5%
40–50	31,8%	56,8%	11,4%
51–60	40,0%	42,7%	17,3%
61 or more	56,5%	27,4%	14,5%

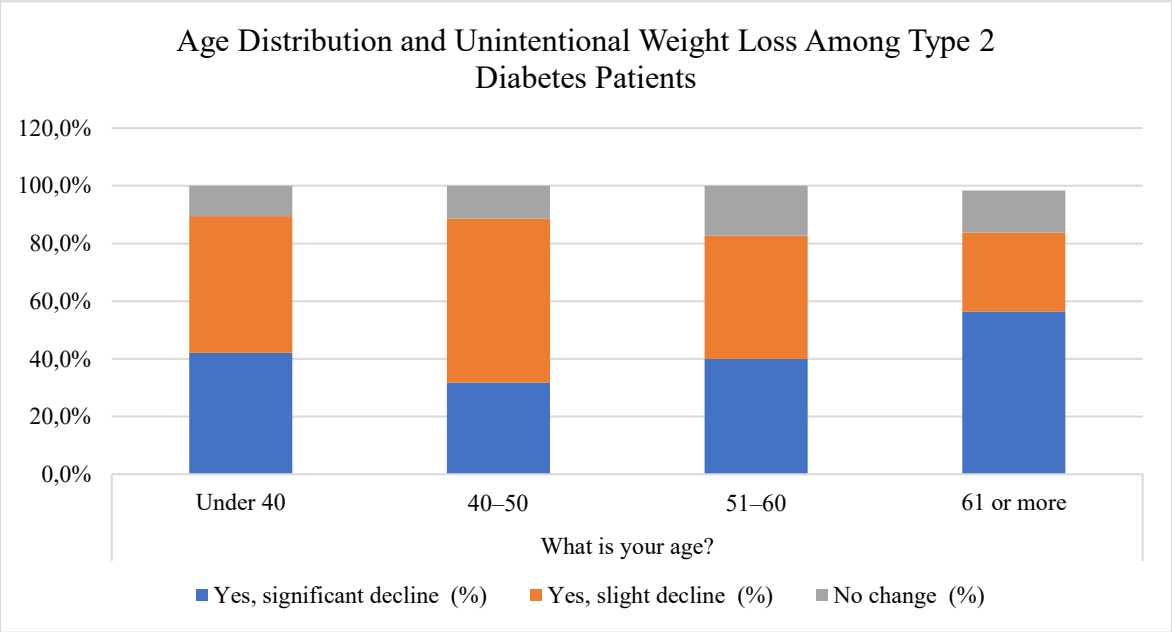

Figure 29 : Age Distribution and Unintentional Weight Loss Among Type 2 Diabetes Patients

Table 7 and **figure 29** examines unintentional weight loss, a sarcopenia marker, across 200 T2DM patients by age. Under 40, 42.1% reported significant decline, 47.4% slight decline, and 10.5% no change, indicating early muscle loss. The 40–50 group showed 31.8% significant, 56.8% slight, and 11.4% no change, peaking in mild decline. At 51–60, 40.0% significant, 42.7% slight, and 17.3% no change reflected a shift to more pronounced loss, while 61 or more peaked at 56.5% significant, 27.4% slight, and 14.5% no change. This age-related increase suggests T2DM exacerbates muscle loss, likely via chronic hyperglycemia and insulin resistance, with the 56.5% at 61+ aligning with peak sarcopenia risk. The 42.1% under 40 indicates early decline

Table 8 : Difficulty Carrying Groceries Weighing About 5 kg

Difficulty level	Frequency	Percentage
0	19	9,5
1	44	22,0
2	36	18,0
3	39	19,5
4	62	31,0
Total	200	100,0

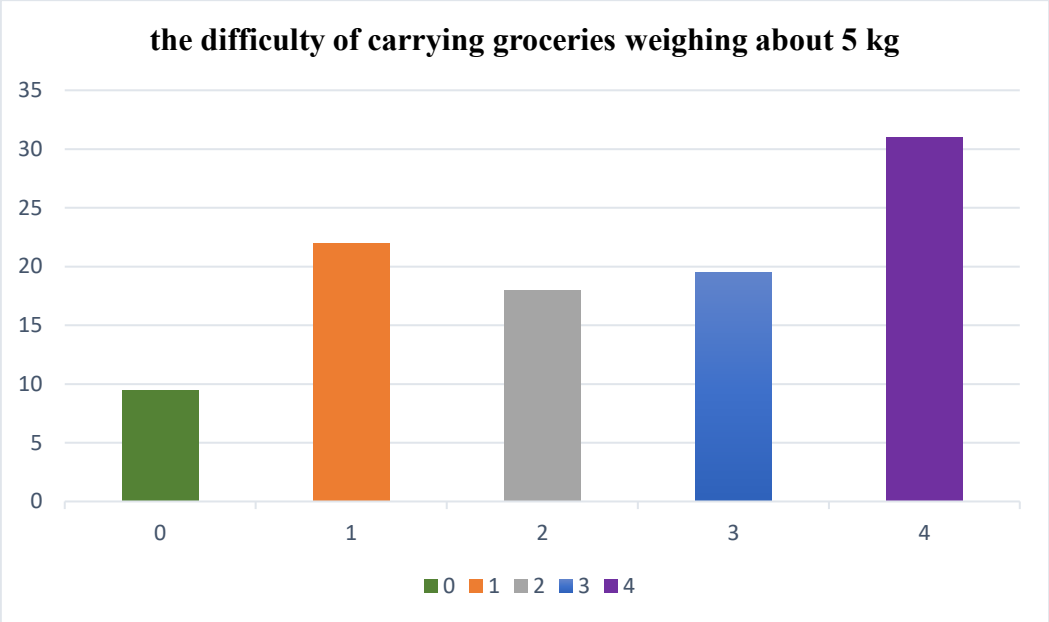

Figure 30 : Difficulty Carrying Groceries Weighing About 5 kg

Table 8 and **figure 30** evaluates the difficulty of carrying 5 kg groceries among 200 T2DM patients, with 9.5% reporting level 0 (very easy), 22.0% level 1, 18.0% level 2, 19.5% level 3, and 31.0% level 4 (very difficult). The 31.0% at the highest difficulty level indicates significant upper body and core muscle impairment, likely driven by T2DM-related sarcopenia, as chronic hyperglycemia and inflammation degrade muscle mass . The 9.5% with no difficulty suggest a subset with early disease or effective management, offering a preventive target

Table 9 : Glycemic Control and Muscle Strength Decline in Type 2 Diabetes Patients

decline in muscle strength or physical function	HbA1c Control			
	Well-controlled (HbA1c <7%)	Moderately controlled (HbA1c 7–8%)	Poorly controlled (HbA1c >8%)	I don't know my recent HbA1c
significant decline	19,5%	25,3%	28,7%	26,4%
slight decline	31,3%	24,1%	19,3%	25,3%
No change	41,4%	20,7%	10,3%	27,6%

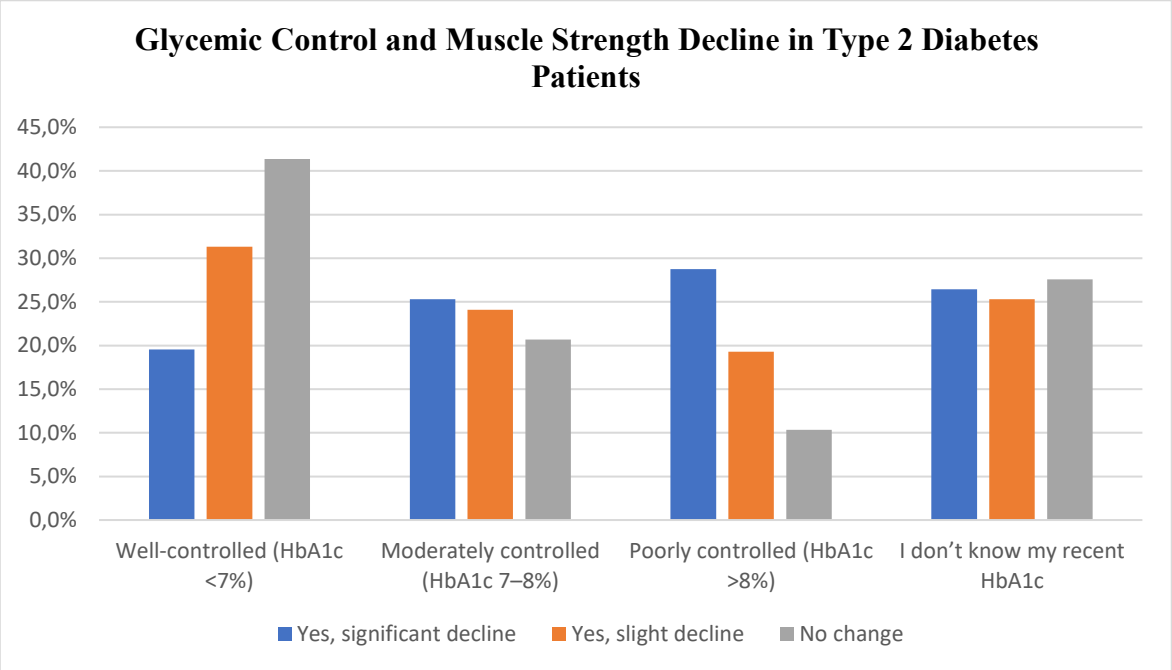

Figure 31 : Glycemic Control and Muscle Strength Decline in Type 2 Diabetes Patients

Table 9 and **figure 31** examines the association between HbA1c control and muscle strength decline in 200 T2DM patients. Among those well-controlled (HbA1c <7%), 41.4% reported no change, 31.3% slight decline, and 19.5% significant decline, indicating preserved muscle function with good glycemic management. Moderately controlled (HbA1c 7–8%) patients showed 20.7% no change, 24.1% slight decline, and 25.3% significant decline,

while poorly controlled (HbA1c >8%) had only 10.3% no change, 19.3% slight decline, and 28.7% significant decline. This 28.7% likely results from chronic

hyperglycemia, which induces oxidative stress and advanced glycation end-products, damaging muscle tissue, and severe insulin resistance, impairing protein synthesis

The People who don't know their recent HbA1c exhibited a mixed profile (27.6% no change, 26.4% significant decline).

This trend supports a bidirectional T2DM-sarcopenia relationship, where poor glycemic control (HbA1c >8%) exacerbates muscle loss, potentially worsened by sarcopenia-induced insulin resistance. The 41.4% no-change rate in well-controlled patients suggests glycemic optimization as a preventive strategy.

Table 10 :Duration of Type 2 Diabetes and Difficulty Climbing Stairs

Duration of T2D	Difficulty level (%)				
	0	1	2	3	4
Less than 5 years	11,4%	20,0%	17,1%	35,7%	15,7%
5–10 years	2,9%	29,4%	20,6%	32,4%	14,7%
More than 10 years	9,4%	20,8%	13,5%	26,0%	30,2%

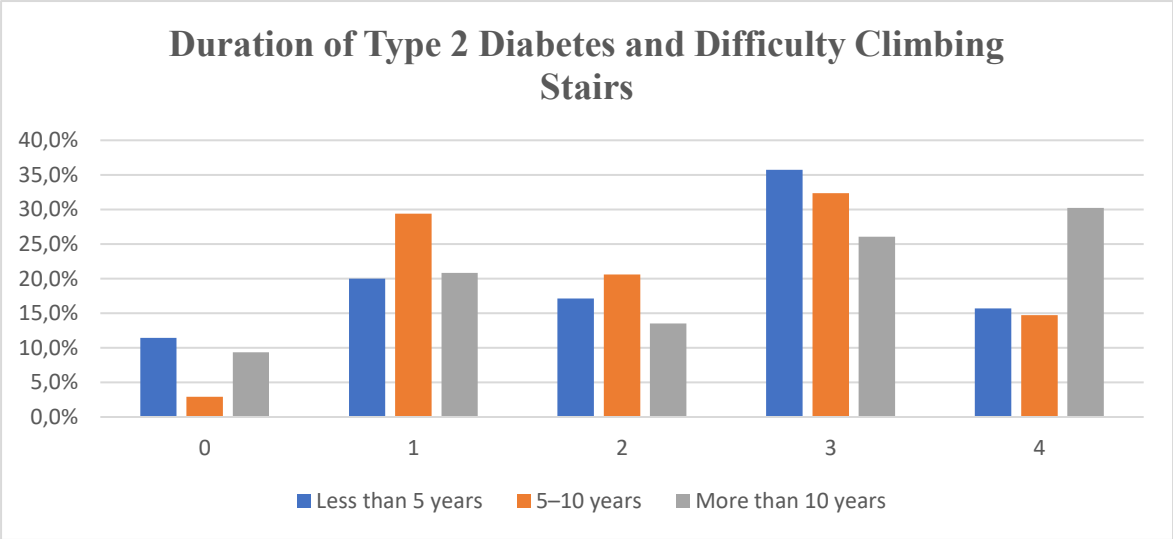

Figure 32 :Duration of Type 2 Diabetes and Difficulty Climbing Stairs

Table 10 and **figure 32** evaluates the impact of T2DM duration on stair-climbing difficulty in 200 patients, with levels 0 (very easy) to 4 (very difficult). For less than 5 years,

35.7% reported level 3 and 15.7% level 4, totaling 51.4% with notable difficulty. The 5–10 years group showed 32.4% at level 3 and 14.7% at level 4 (47.1%), while more than 10 years peaked at 30.2% at level 4 and 26.0% at level 3 (56.2%). The higher 35.7% at level 3 for <5 years may reflect early metabolic stress and poor glycemic control, causing acute moderate impairment, while longer durations shift difficulty to severe levels (30.2% at >10 years) due to chronic muscle damage from hyperglycemia. This progression supports a bidirectional T2DM-sarcopenia relationship, where initial muscle loss drives insulin resistance, and prolonged disease exacerbates sarcopenia.

Table 11 : Awareness of Sarcopenia Among Type 2 Diabetes Patients

Response	Frequency	Percentage
Yes	10	5,0
No	190	95,0
Total	200	100,0

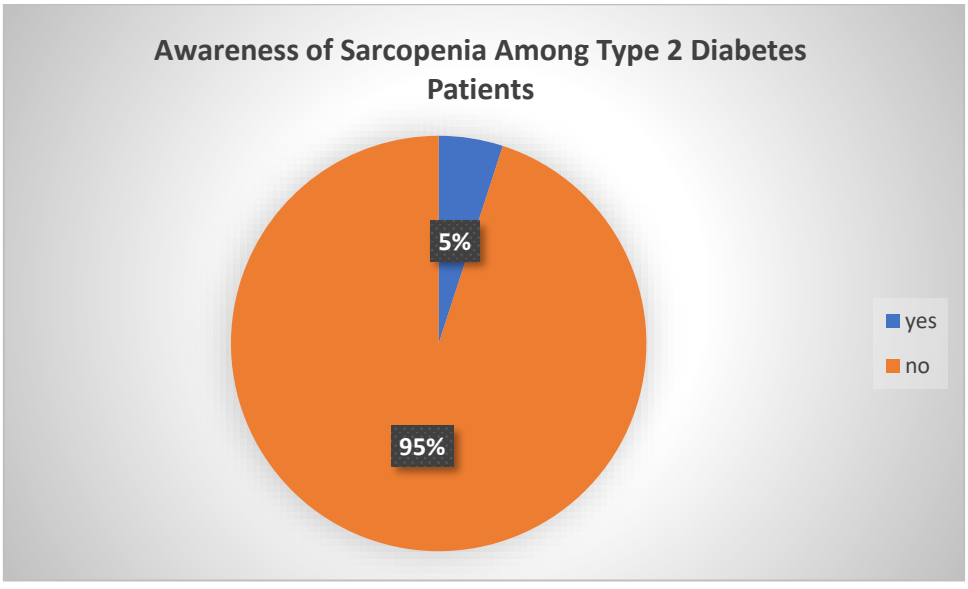

Figure 33 : Awareness of Sarcopenia Among Type 2 Diabetes Patients

Table 11 and **figure 33** assesses awareness of sarcopenia among 200 T2DM patients, with only 5.0% familiar with the term and 95.0% unfamiliar. The 95.0% lack of familiarity indicates a significant knowledge gap, potentially preventing patients from recognizing and

addressing muscle loss, a key complication of T2DM that can exacerbate insulin resistance and glycemic control . The 5.0% aware group may represent a minority proactive in managing their health, offering a foundation for educational efforts.

Table 12 : Perceptions of Muscle Strengthening in Diabetes Management Among Type 2 Diabetes Patients

Response	Frequency	Percentage
I don't know	164	82,0
Yes, I know some methods (such as exercise, nutrition, or supplements)	12	6,0
Yes, and I'd like to know more	23	11,5
I don't think it's related	1	0,5
Total	200	100,0

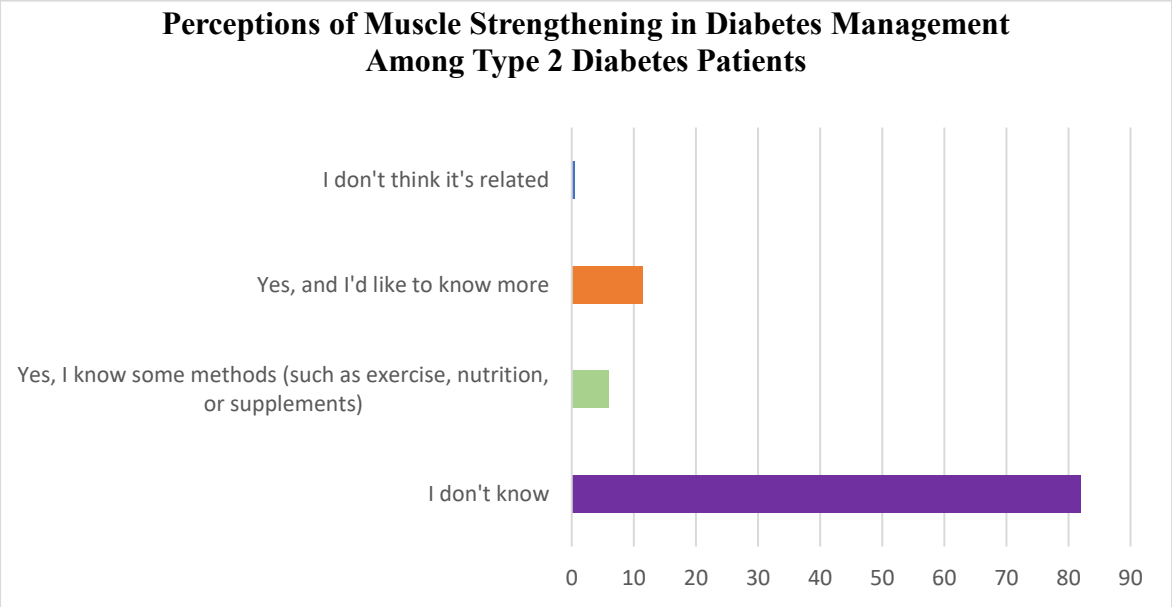

Figure 34 : Perceptions of Muscle Strengthening in Diabetes Management Among Type 2 Diabetes Patients

Table 12 and **figure 34** evaluates awareness of muscle strengthening's role in T2DM management among 200 patients, with 82.0% unsure, 6.0% knowing some methods (e.g., exercise, nutrition, supplements), 11.5% believing it helps and wanting to know more, and 0.5% dismissing its relevance. The 82.0% "I don't know" indicates a significant knowledge gap, potentially preventing patients from using muscle strengthening to improve insulin

sensitivity and glycemic control. The 17.5% with some awareness or interest suggest a subgroup that could benefit from education to prevent sarcopenia, where muscle loss exacerbates T2DM

Final Discussion

The findings of this study underscore a robust and clinically significant **bidirectional relationship between type 2 diabetes mellitus (T2DM) and sarcopenia**. Across multiple domains—glycemic control, functional status, disease duration, age, comorbidities, physical activity, nutrition, and awareness—evidence consistently points to a reciprocal interplay where T2DM accelerates muscle mass and function decline, while sarcopenia exacerbates metabolic dysfunction.

Poor glycemic control, particularly HbA1c levels >8%, was associated with the highest rates of significant muscle strength decline. This supports the hypothesis that chronic hyperglycemia promotes oxidative stress, inflammation, and advanced glycation end-product accumulation—all contributing to muscle catabolism. Conversely, individuals with well-controlled HbA1c levels (<7%) showed the highest preservation of muscle function, suggesting that tight glucose regulation may be protective against sarcopenia development.

Longer duration of T2DM correlated with increased physical impairment, notably in activities such as stair climbing and carrying objects—hallmark indicators of sarcopenic progression. Even within the first five years of diagnosis, over 50% of participants reported moderate-to-severe difficulty, implying that muscle deterioration can begin early in the disease course.

Age stratification further revealed that muscle decline was not confined to older adults. Although individuals aged 61+ exhibited the most pronounced muscle loss, a substantial proportion of younger patients (<40 years) also reported significant declines, pointing to early-onset sarcopenia potentially driven by metabolic dysregulation and lifestyle factors such as physical inactivity and inadequate protein intake.

The prevalence of comorbid conditions—especially hypertension and obesity—highlights the synergistic effect of multiple chronic conditions on functional capacity. These comorbidities not only contribute to systemic inflammation but may also compound the burden of sarcopenia and T2DM, creating a vicious cycle of deteriorating muscle and metabolic health.

Alarmingly, only 5% of participants were aware of the term “sarcopenia,” and 82% lacked understanding of the role of muscle strengthening in diabetes management. This lack of awareness reflects a critical gap in patient education and healthcare messaging, undermining prevention efforts. Furthermore, 64% reported not engaging in any form of exercise, and over half were either unsure or did not consume sufficient protein—two modifiable factors essential for both glycemic control and muscle preservation.

Taken together, these data affirm that **T2DM and sarcopenia exist in a deleterious feedback loop**: poor glycemic control accelerates muscle loss, and sarcopenia impairs insulin sensitivity, perpetuating hyperglycemia. Breaking this cycle requires integrated, multidisciplinary interventions that prioritize:

- **Early screening** for muscle weakness and functional decline in diabetic patients of all ages.
- **Education** on the role of protein intake and resistance training in preserving muscle health.
- **Targeted lifestyle interventions**, including structured exercise programs and nutritional counseling.
- **Improved awareness** of sarcopenia among both patients and healthcare providers to foster proactive management.

CONCLUSION AND PERSPECTIVES

Conclusion

This study highlights a strong bidirectional relationship between type 2 diabetes mellitus (T2DM) and sarcopenia. Poor glycemic control accelerates muscle loss through chronic inflammation, oxidative stress, and metabolic dysfunction. Conversely, decreased muscle mass impairs glucose uptake, exacerbating insulin resistance and worsening diabetes management. Functional decline was evident even in younger patients and early stages of the disease, underscoring the need for early intervention. Comorbidities such as hypertension and obesity further compound this cycle. Low awareness of sarcopenia and inadequate engagement in exercise and protein intake were prevalent. These findings emphasize the need for integrated approaches that combine glycemic management with muscle-preserving strategies. Education on resistance training and nutritional support is critical. Routine screening for sarcopenia in T2DM patients should be prioritized. Breaking this vicious cycle can enhance metabolic health and prevent disability in diabetic populations.

Recommendations

To address the bidirectional relationship between type 2 diabetes mellitus (T2DM) and sarcopenia, several clinical and public health actions are recommended. First, routine screening for sarcopenia should be integrated into diabetes care using validated tools such as the SARC-F questionnaire, handgrip strength, and gait speed assessments. Early identification is critical, as muscle decline was observed even in younger individuals and those with recent T2DM diagnoses. Second, structured resistance and strength training programs should be promoted, as they are effective in improving muscle mass, enhancing insulin sensitivity, and stabilizing glycemic control. Alongside exercise, adequate dietary protein intake—ideally 1.0 to 1.2 g/kg/day—should be emphasized to support muscle protein synthesis and counteract catabolic processes.

Patient education plays a pivotal role and should focus on raising awareness about the impact of muscle loss in diabetes, the benefits of physical activity, and the importance of protein-rich nutrition. Given that physical inactivity was highly prevalent among participants, strategies to reduce sedentary behavior must be implemented, including accessible and culturally appropriate exercise interventions. A multidisciplinary approach is essential, involving endocrinologists, dietitians, physiotherapists, and exercise specialists to provide comprehensive care. Additionally, effective management of comorbidities such as hypertension and obesity is crucial to mitigate systemic inflammation and reduce sarcopenia

risk. Finally, national diabetes and geriatric guidelines should incorporate specific recommendations for sarcopenia screening and management. Ongoing research and policy support are needed to further understand this interaction and to develop scalable interventions that target both metabolic and musculoskeletal health.

PART V.
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ANNEXES

III.1. Survey on sarcopenia and T2D

Survey on sarcopenia and T2DM

Thank you for taking the time to participate in this questionnaire. The purpose of this survey is to explore the relationship between Type 2 Diabetes (T2DM) and muscle health, particularly sarcopenia (age- or disease-related muscle loss). Your responses will help in understanding how diabetes affects muscle function and overall well-being.

Please answer the questions as accurately as possible. If a question does not apply to you, feel free to skip it.

Section 1: General Information & Health Background

1. What is your age?

☐ Under 40 ☐ 40–50 ☐ 51–60 ☐ 61 or more

2. What is your gender?

☐ Male ☐ Female

3. How long have you been diagnosed with Type 2 Diabetes?

☐ Less than 5 years ☐ 5–10 years ☐ More than 10 years

4. How well-controlled is your blood sugar based on your most recent HbA1c test?

☐ Well-controlled (HbA1c <7%) ☐ Moderately controlled (HbA1c 7–8%)

☐ Poorly controlled (HbA1c >8%) ☐ I don't know my recent HbA1c

5. Do you have any other health conditions? (Select all that apply)

☐ High blood pressure ☐ Heart disease ☐ Osteoporosis ☐ Kidney disease

☐ Obesity ☐ None ☐ Other (Specify: _____)

6. Have you experienced significant unintentional weight loss in the past 12 months?

☐ Yes, more than 5 kg ☐ Yes, between 2–5 kg ☐ No noticeable weight loss

Section 2: Muscle Health and Physical Function

1. Have you noticed a decline in your muscle strength or physical function in the past 5 years?

☐ Yes, significant decline ☐ Yes, slight decline ☐ No change

2. On a scale of 1–5, how difficult is it for you to climb a flight of stairs? (1 = Very easy, 5 = Very difficult)

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

3. On a scale of 1–5, how difficult is it for you to carry groceries weighing about 5 kg? (1 = Very easy, 5 = Very difficult)

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Section 3: Physical Activity and Lifestyle

1. Do you exercise?

☐ yes ☐ No

2. Do you feel your diet includes enough protein-rich foods (e.g., meat, eggs, beans)?

☐ Yes ☐ No ☐ Unsure

Section 4: Sarcopenia Awareness and Treatment

1. Are you familiar with the term 'sarcopenia' (age- or disease-related muscle loss)?

☐ Yes ☐ No

2. Has your doctor ever discussed sarcopenia or muscle loss with you?

☐ Yes ☐ No

3. If yes, where did you learn about sarcopenia?

☐ Doctor/Healthcare provider ☐ Internet/Medical websites

☐ Family/Friends ☐ Other (Specify: _____) ☐ Not applicable (not familiar)

4. Do you think muscle strengthening helps treat diabetes? Do you know or apply any methods for this?

☐ I don't know ☐ Yes, I know some methods (such as exercise, nutrition, or supplements) ☐ Yes, and I'd like to know more ☐ I don't think it's related

III.2. Online questionnaire:

https://forms.gle/kXQu5Ko8eLbASKVN8