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Theme

Obesity a risk factor for type 2 diabetes

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Supported on:

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College year 2022/2023

Dedication

I dedicate this modest work

To the man of my life, my eternal example, my moral support and source of joy and happiness, the one who has always sacrificed himself for me

See succeed, May God keep you for us, my father. I love you.

To the light of my days, the source of my efforts, the flame of my heart, my life and my happiness; Mom I love you infinitely.

To the little prince of the family: Mohamed rayane.

To my dear brothers and sisters: Yassine, Reda

Meriem; Ikram and Wiam to whom I wish a long life

full of health and success.

To all my friends: Ghalia; Ahlam;Nadia;Hiba; Houda ; Oum-Elkhir and Bakhtamemories, happy moments spent together,

with My sincere desires for success, happiness, health and prosperity.

Thank you to all the other people I knew but didn't mention.

ALLALI Narimane

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To all my friends memories, happy moments spent together, with My sincere desires for success, happiness, health and prosperity.

Thank you to all the other people I knew but didn't mention.

BELAKHDAR Fatima Zahra.

Abstract

The diabetes is a group of metabolic diseases characterized by chronic hyperglycemia that follows a defect in insulin secretion, insulin action, or insulin resistance. The aging of the population, the westernization of food, sedentarization are all factors that have triggered the development of obesity, fertile ground for the installation of type 2 diabetes. Obesity is manifested by an excess abnormal body fat, especially visceral fat caused by calorie consumption exceeding energy expenditure, leading to a direct effect on health and increasing the risk of diseases such as diabetes, hypercholesterolemia or high blood pressure. Obesity and diabetes rates have risen dramatically over the past few decades and the prevalence is expected to continue to rise in the years to come. The link between obesity and the development of type2 diabetes remains a higher risk, well established and supported by several studies and numerous observations.

In order to establish the relationship between type 2 diabetes and obesity, an analytical epidemiological study was carried out on 510 type 2 diabetic patients at the LES FRERES CHENAFA hospital in the Wilaya of NAAMA.

Following our survey, a large number of diabetic patients have a genetic background for diabetes, which increases the individual risk.

The study shows that women make up 69.41% of the population, with a higher prevalence of Type II diabetes. Males are less likely to consult, and Type II diabetes is now equally prevalent. The majority of patients have diabetes for 0-20 years. A survey found that 28% of 140 hypertensive subjects have diabetes, mainly due to unhealthy diet, inactivity, overweight, and stress. Women are more affected due to insufficient exercise, while men are less affected. Most patients take oral diabetes medication, 15% take insulin, and 20% combine both. Women between 50 and 70 are the most vulnerable, with a 75.12% rate.

Adopting an unhealthy lifestyle will give diabetes a chance to set in, so regular exercise and a healthy diet can help maintain blood sugar levels, prevent complications, reduce weight loss, and possibly reverse diabetes altogether.

Keywords: obesity, Body weight, type 2 diabetes, NAFLD, insulin resistance, lipotoxicity.

الملخص

مرض السكري هو مجموعة من الأمراض الأيضية التي تتميز بفرط سكر الدم المزمن الذي يتبع خللًا في إفراز الأنسولين أو عمل الأنسولين أو مقاومة الأنسولين. شيخوخة السكان ، وتغريب الطعام ، والتوطين كلها عوامل أدت إلى تطور السمنة ، وأرض خصبة لتركيب مرض السكري من النوع 2. تتجلى السمنة من خلال الدهون الزائدة غير الطبيعية في الجسم ، وخاصة الدهون الحشوية الناجمة عن استهلاك السعرات الحرارية تجاوز نفقات الطاقة ، مما يؤدي إلى تأثير مباشر على الصحة ويزيد من مخاطر الإصابة بأمراض مثل السكري أو ارتفاع نسبة الكولسترول في الدم أو ارتفاع ضغط الدم. ارتفعت معدلات السمنة ومرض السكري بشكل كبير خلال العقود القليلة الماضية ومن المتوقع أن يستمر انتشاره في الارتفاع في السنوات القادمة. لا يزال الارتباط بين السمنة وتطور مرض السكري من النوع 2 يمثل خطرًا أكبر، وهو راسخ ومدعوم بالعديد من الدراسات والملاحظات العديدة.

من أجل إثبات العلاقة بين مرض السكري من النوع 2 والسمنة، تم إجراء دراسة وبائية تحليلية على 510 مرضى السكري من النوع 2 في مستشفى LES FRERES CHENAFA بولاية NAAMA.

وفقًا لمسحنا، فإن عددًا كبيرًا من مرضى السكري لديهم خلفية وراثية لمرض السكري، مما يزيد من المخاطر الفردية.

أظهرت الدراسة أن النساء يمثلن 69.41٪ من السكان ، مع انتشار أعلى لمرض السكري من النوع الثاني. تقل احتمالية استشارة الرجال ، كما أن داء السكري من النوع الثاني أصبح شائعًا الآن. غالبية المرضى يعانون من مرض السكري من 0 إلى 20 عامًا. كشفت دراسة استقصائية أن 28٪ من 140 شخصًا يعانون من ارتفاع ضغط الدم يعانون من مرض السكري، ويرجع ذلك أساسًا إلى سوء التغذية وقلة النشاط وزيادة الوزن والإجهاد. تتأثر النساء أكثر بسبب عدم كفاية التمارين البدنية ، في حين أن الرجال أقل تضررا. يتناول معظم المرضى أدوية السكري عن طريق الفم ، ويتناول 15٪ الأنسولين و 20٪ يجمعون بين الاثنين. النساء بين 50 و 70 هم الأكثر ضعفا بنسبة 75.12٪.

سيعطي تبني نمط حياة غير صحي فرصة لمرض السكري ، لذا فإن ممارسة الرياضة بانتظام واتباع نظام غذائي صحي يمكن أن يساعد في الحفاظ على مستويات السكر في الدم ، ومنع المضاعفات ، وتقليل فقدان الوزن ، وربما عكس مرض السكري تمامًا.

الكلمات المفتاحية: السمنة ، وزن الجسم ، السكري من النوع 2 ، NAFLD ، مقاومة الأنسولين ، السمنة الدهنية.

Résumé

Le diabète est un groupe de maladies métaboliques caractérisées par une hyperglycémie chronique qui fait suite à un défaut de sécrétion d'insuline, d'action de l'insuline ou de résistance à l'insuline. Le vieillissement de la population, l'occidentalisation de l'alimentation, la sédentarisation sont autant de facteurs qui ont déclenché le développement de l'obésité, terreau fertile à l'installation du diabète de type 2. L'obésité se manifeste par un excès anormal de graisse corporelle, notamment de graisse viscérale provoqué par une consommation calorique supérieure à la dépense énergétique, entraînant un effet direct sur la santé et augmentant le risque de maladies telles que le diabète, l'hypercholestérolémie ou l'hypertension artérielle. Les taux d'obésité et de diabète ont augmenté de façon spectaculaire au cours des dernières décennies et la prévalence devrait continuer à augmenter dans les années à venir. Le lien entre l'obésité et le développement du diabète de type 2 reste un risque plus élevé, bien établi et étayé par plusieurs études et de nombreuses observations.

Afin d'établir la relation entre le diabète de type 2 et l'obésité, une étude épidémiologique analytique a été réalisée sur 510 patients diabétiques de type 2 à l'hôpital LES FRERES CHENAFA de la Wilaya de NAAMA.

Suite à notre enquête, un grand nombre de patients diabétiques ont un bagage génétique pour le diabète, ce qui augmente le risque individuel.

L'étude montre que les femmes représentent 69,41% de la population, avec une prévalence plus élevée de diabète de type II. Les hommes sont moins susceptibles de consulter et le diabète de type II est maintenant également répandu. La majorité des patients sont diabétiques depuis 0 à 20 ans. Une enquête a révélé que 28 % des 140 sujets hypertendus souffraient de diabète, principalement en raison d'une mauvaise alimentation, de l'inactivité, du surpoids et du stress. Les femmes sont plus touchées en raison d'un exercice physique insuffisant, tandis que les hommes sont moins touchés. La plupart des patients prennent des médicaments oraux contre le diabète, 15 % prennent de l'insuline et 20 % combinent les deux. Les femmes entre 50 et 70 ans sont les plus vulnérables, avec un taux de 75,12 %.

Adopter un mode de vie malsain donnera au diabète une chance de s'installer, donc l'exercice régulier et une alimentation saine peuvent aider à maintenir la glycémie, à prévenir les complications, à réduire la perte de poids et éventuellement à inverser complètement le diabète.

Mots clés : obésité, poids corporel, diabète de type 2, NAFLD, résistance à l'insuline, lipotoxicité.

Liste of abbreviations :

4E-BP1: 4E binding protein 1.

ADO: Aural Antidiabetic.

ATP: Adenositis triphosphate.

BMI: body mass index.

Camp/PKA: cyclic adenosine monophosphate/protein kinase A.

DAG: diacylglycerols.

DID: D insulin-dependent iabetus.

ERK: extracellular signal-regulated kinase.

GD: Gestational diabetes.

GLUT: Glucose transporters.

Grb2: growth factor receptor-bound protein 2.

GSK3: glycogen synthase 3 kinase.

HbA1c: glycated hemoglobin A.

HDL: high-density lipoproteins.

IDF: International Diabetes Federation.

IR: insulin receptor.

IR: Insulin resistance.

LDL: low-density lipoprotein.

MD: Diabetes mellitus.

MODY: Maturity Onset Diabetes in the Young.

MPA: Adenositemonophosphate.

MTOR: mammalian target of rapamycin.

NAFLD: non-alcoholic fatty liver disease.

NDDG: National Diabetes Data Group.

NIDDM: non-insulin-dependent diabetes mellitus.

PDK1/2: 3-phosphoinositide-dependent protein kinase ½.

PH domain: domain of homology with pleckstrin.

PKB: protein kinase B

PP: Pancretan polypeptide.

PTB: phosphotyrosine binding.

SH2: src homology 2.

SHC: src homologous and collagen protein.

SHP2: SH2 domain protein tyrosine phosphatase-2.

T2DM: type 2 diabetes mellitus.
IDDM: insulin-dependent diabetes mellitus.

TGO: GLUTAMATE-OXALOACETATE-TRANSAMINASE.

TGP: GLUTAMATE-PYRUVATE TRANSAMINASE.

TIDM: Type I diabetes mellitus.

TNF-*α:* TumorNecrosis Factor-α..

WHO: World Health Organization.

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INTRODUCTION

Introduction :

In 1964, according to the World Health Organization **(WHO)**, "health is a complete state of physical, mental and social well-being, and not merely the absence of disease or infirmity". Health is considered "one of the fundamental rights of every human being" and is "a fundamental condition for world peace and security". It follows that the good social and medical health of populations is essential for stability at the international level **(Boyarkine, C,2021)**

In 1679, a Swiss medical researcher ***J-C. Brunner***, studying the action of the Pancreas on digestion, noted that the pancreatectomy dog was thirsty and hungry, but it did not possess signs of diabetes .

In 1855, ***Claude Bernard***, shows that blood sugar remains constant regardless of food; he describes the role of the liver in storing glucose in the form of glycogen (animal starch) and can convert it into glucose, and shows that glycosuria (the presence of glucose in the urine without hyperglycemia) is only a symptom and does not present the disease herself; diabetes. In Strasbourg, in April 1889, ***Von Mering***, studied the digestion of fats, ***Minkowski*** performed a pancreatectomy and discovered that the dog had become diabetic, so the pancreas acted on the assimilation of sugars.

In 1869, the German pathologist ***Paul Langerhans*** described two types of cells without knowledge of their functions. ***Laguesse*** who knows the thesis supported by ***langerhans*** describing, there are among the pancreatic glandular tissue, cells polygonals grouped in small clusters, shows their epithelial nature, the signaments provisionally under the name -islets of Langerhans- and located there the internal secretion of the pancreas, in 1909 ***Jean de Meyer***, in Brussels, considers that one could give a name to the secreted substance; he called it insulin.

Nicolas Paulesco, a Roman professor, shows that, in a dog made diabetic by pancreatectomy, the intravenous injection of a pancreatic extract he calls "Pancrein" causes a decrease in hyperglycemia and sometimes even hypoglycemia. In 1921, ***Frederick Grant Banting***, discovered insulin supposing that the pancreas could in addition to its exocrine function (secretion of enzymes acting on the digestion) and have an endocrine function: production of a hormone by the islets of langerhans able to regulate blood sugar, the professor of physiology ***Mac Leod*** with the help of Best Canadian of 22 years graduated in physiology and biochemistry and medical student, test the pancreatic extracts obtained, on dogs made diabetic by pancreatectomy thanks to the help of the Collip the biochemist, they obtain extracts with hypoglycemic effects.

Leonard Thompson, the first diabetic patient, in 1922, is treated with a preparation obtained by alcoholic extraction of the beef pancreas, during the summer of 1922, the manufacture of insulin is done on a large scale and from 1923 it will be available.

Insulin will then be "the protein of the twentieth century". It is a real miracle for diabetic patients, but also for researchers. The Nobel Prize is given to all three:

- To ***Banting*** and ***Mac Leod*** for the first protein for therapeutic protein use.
- To ***Frederick Sanger*** for the first determination of the sequence of a protein.
- To ***Rosalyn Yalow*** in 1977 for the first radioimmunoassay **(REDJEM, Mayar et *al*, 2022).**

The objective of our study is to highlight the incidence of type II diabetes and the determination of risk factors and complications associated with this pathology.And on the other hand to make a comparison of some biochemical parameters such as (Glycemia, HbA1C, Total cholesterol, HDL, LDL, Triglyceride, Crea, M-Albumin, TGO, TGP), and also treatment parameters use patients to combat the evolution of T2DM.

For this we will carry out a study on 510 people with T2DM with complications.

CHAPTER I :
DEFINNITION OF DIABETES AND RISK FACTORS

I/1 Definition of diabetes :

Diabetes is defined as hyperglycemia occurring when the amount of plasma insulin is no longer sufficiently produced and/or active enough in relation to the bodies needs **(Tenenbaum, Mathie, et *al*, 2018)**. Diabetes is a syndrome characterized by an elevation of blood sugar above normal values that can lead to specific metabolic and tissue complications **(RYAD, BOUABDALLAH et *al*, 2020)**.

Indeed, this disease develops when the pancreas does not produce enough insulin – this is type 1 diabetes, which requires injections of this hormone regulating the concentration of glucose in the blood **(Glycemia)** – or when the body does not use it properly. The insulin produced; this is called type 2 diabetes, for which treatment involves medication but may also require insulin **(Bauduceau, Bernard et *al*, 2017).**

I/1.1. Prevalence and epidemiology :

Diabetes mellitus is a global public health problem and particularly in sub-Saharan Africa, where the ever-increasing prevalence is a major concern. In these countries, this expansion is part of a real epidemiological transition from communicable to non-communicable diseases due not only to population ageing, physical inactivity and obesity, but also to endocrine disruptors. The circumstances of discovery of the disease vary from one country to another depending on the degree of medicalization and the level of interest of populations in health problems, and are dominated by classic symptoms **(Nemi, Komi Dzidzonu, et *al*, 2019).**

More than 50% of diabetics have at least one family member with the disease and 56.7% are obese.

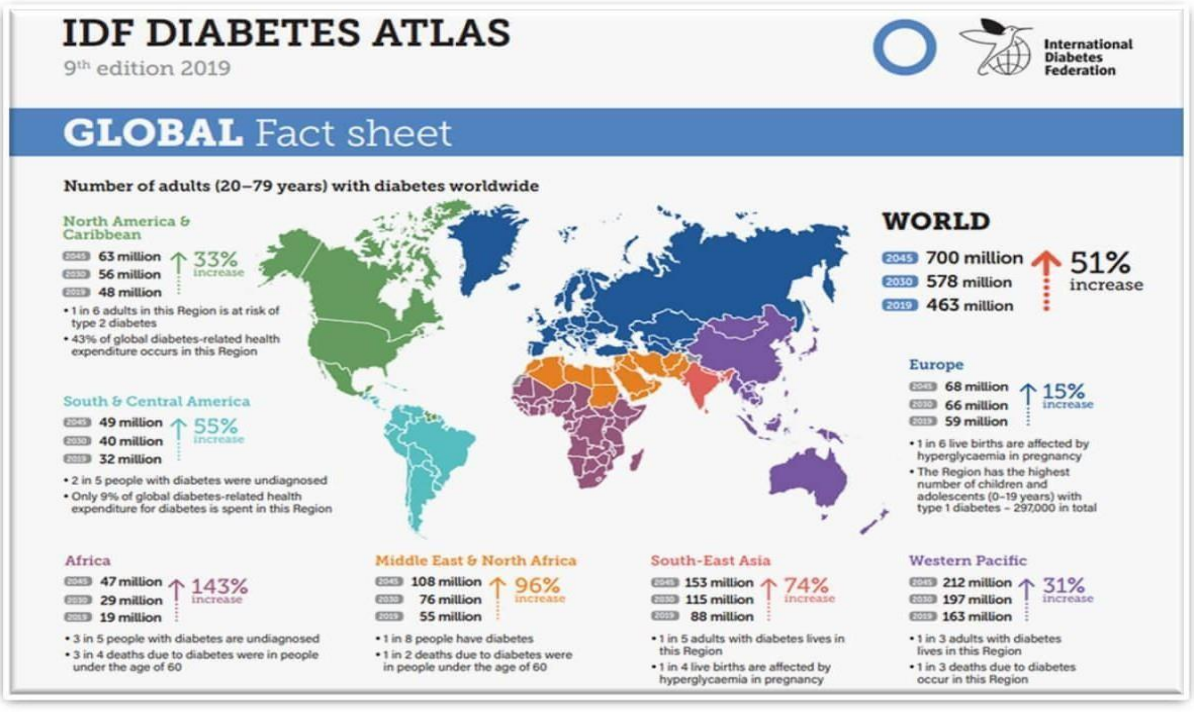


Figure 01 : Estimated number of people with diabetes worldwide in 9th edition 2019 (20-79 years) **("IDF DIABETES ATLAS" (2019).**

- **In Algeria:** Diabetes is a public health problem both in the world and in Algeria, In Algeria, diabetes remains a worrying reality since it is the second chronic disease after hypertension. The number of diabetics in Algeria has increased from one million people in 1993, to more than 2,500,000 in 2007, or 10% of the population in 2010 **(Dali-Sahi, M, et *al*, 2012).**

According to a national survey, named Transition and Health Impact in North Africa **(TAHINA)** carried out in 2005 by the National Institute of Public Health of Algiers **(INSP)** diabetes is the second most common morbid condition (8.78%) after high blood pressure(16,23) in Algeria. It affects 12.21% Algerians including a female predominance of 12.54% **(Salemi, Ouassila, 2010).**

More than 50% of diabetics have at least one family member with the disease and 56.7% are obese. Screening for type 2 diabetes is now a priority. In order to facilitate its detection and to consider prevention, it is essential to update the underlying factors **(Dali-Sahi, M, et *al*, 2012).**

I/2. Classification of diabetes:

The first classification of diabetes was published in 1979 by (NDDG). And amended in 1985 by (WHO). This NDDG classification of MD was based on applied pharmacological therapy and divided into two broad groups: insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM). The NDDG also DM subclassified into (a) gestational diabetes (b) diabetes mellitus related to malnutrition and a few other types.

The new classification is based on the pathogenesis of the disease, not its treatment. Four broad categories were proposed, Type I diabetes mellitus (TIDM) and type 2 diabetes mellitus (T2DM), other specific types of diabetes and gestational diabetes **(TOUATI, Rachida, et *al*, 2021)**.

I/2.1. Type 1 diabetes :

Encompasses diabetes that is primarily a result of pancreatic beta cell destruction with consequent insulin deficiency, which is prone to ketoacidosis. This form includes cases due to an autoimmune process and those for which the etiology of beta cell destruction is unknown **(Punthakee, Zubin et *al*, 2018)**.

Patients with T1D are always treated with insulin; basal insulin secretion is substituted by one or two injections of slow insulin or intermediary **(Cheisson, Gaëlle, et *al*, 2017)**.

I/2.2. Type 2 diabetes :

Type 2 diabetes (called non-insulin-dependent diabetes or adult diabetes), results from the effective use of insulin by the body **(mondiale de la Santé, Organisation, 2016)**.

I/2.3. Gestational diabetes :

The World Health Organization (WHO) defines gestational diabetes as «A carbohydrate tolerance disorder leading to hyperglycemia of varying severity, beginning or first diagnosed during pregnancy, regardless of the necessary treatment and evolution in the postpartum period. Two situations must be considered: latent diabetes which is revealed by pregnancy and persists after childbirth, and an abnormality of carbohydrate tolerance which disappears,

at least temporarily, postpartum **(Henri, E, et *al*, 2020)**.

I/2.4. Other specific types of diabetes:

Includes a wide variety of relatively uncommon disorders, especially diabetes that is genetic in origin or associated with other diseases, or the use of certain medicaments. Including latent autoimmune diabetes in adults, a term used to describe the small number of people who have apparent type 2 diabetes and in whom it appears there is a loss of immune-mediated pancreatic beta cells **(MESSAAD, Wahiba et *al*, 2022)**.

There are also rarer types for example: MODY (Maturity Onset Diabetes in the Young), generally non-insulin-dependent. Are strongly determined by a genetic component **(NARIMENE, BOUHAIK et *al*, 2021)**.

- **a. Mitochondrial Diabetes:** Maternally Innherited Diabetes and Deafnes MIDD, is a point mutation of mitochondrial DNA at position 3243 leading to ATP deficiency causing a decrease in insulin secretion **(REDJEM, Mayar et *al*, 2022)**.
- **b. Diabetes Medicine:** Most drugs can cause glucose intolerance, for examples: Corticosteroids, Combined estrogen-progestogens, Thiazide diuretics, Diazoxide and Propranolol **(BELFAR, Karima et *al*, 2020)**.

I/3 Anatomical and histological organization of the pancreas:

I/3.1. Anatomical of the pancreas:

The pancreas is an elongated organ, in direct communication with the digestive tract. Its exocrine function is essential for the digestion of food, and its endocrine function is at the origin of the synthesis of the main hormones that control the blood sugar of the body. Dysfunctions of this organ are the cause of serious pathologies, such as diabetes, pancreatitis and pancreatic adenocarcinoma **(Bessaguet, Flavien et *al*, 2021)**.

The pancreas (meaning all flesh) lies in the upper abdomen behind the stomach. The pancreas is part of the gastrointestinal system that makes and secretes digestive enzymes into the intestine, and also an endocrine organ that makes and secretes hormones into the blood to control energy metabolism and storage throughout the body **(Longnecker, Daniel S, 2014).**

It is worthwhile to mention a few definitions for key terms as used in the context of the pancreas: Exocrine pancreas and Endocrine pancreas **(Longnecker, Daniel S, 2014)**.

The human pancreas is a well-defined solitary organ. Macroscopically, it can be divided into4 main parts: head, neck, body and tail **(TOUATI, Rachida, et *al*, 2021)**.

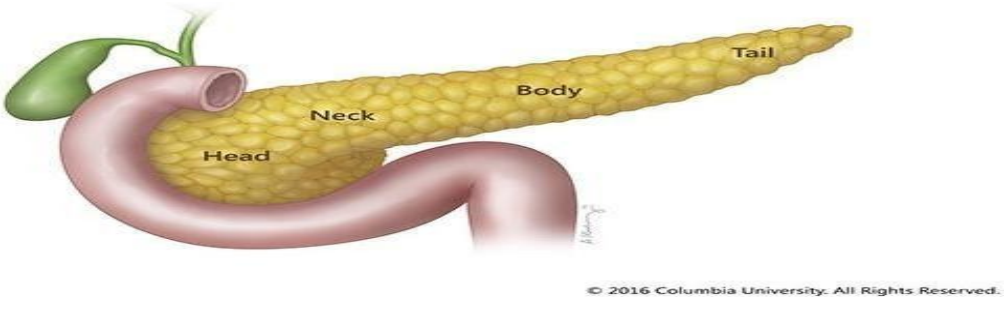


Figure 02: Diagram showing the shape and parts of the pancreas **(Columbia University Irving Medical Center, 1999-2022)**

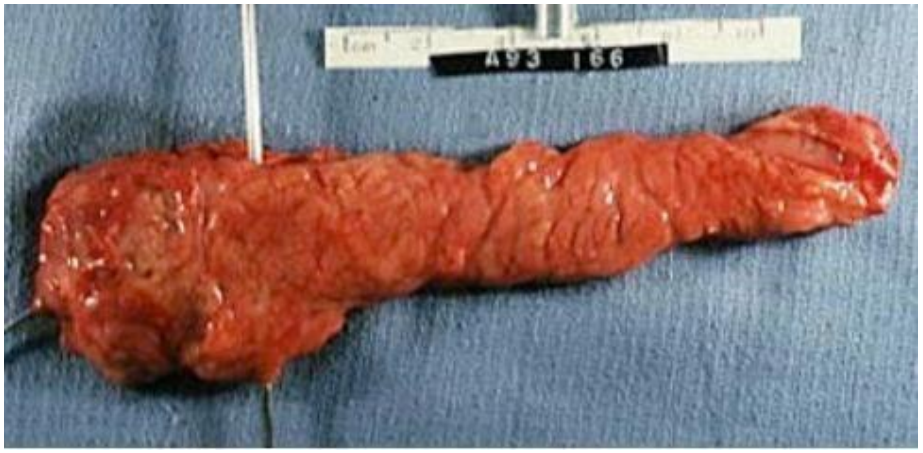


Figure 03: photographic representation of human Pancreas **(Columbia University Irving Medical Center, 1999-2022)**.

I/4 Physiology of the pancreas:

The pancreas is composed of two distinct components: the exocrine pancreas, a reservoir digestive enzymes, and endocrine islets, source of insulin, a metabolic hormone Vital **[10]**.

I/4.1.Endocrine function:

- **Endocrine pancreas :**

Most islets *(islets of Langerhans)* that collectively comprise the endocrine pancreas are too small to be seen by gross examination, and thus they we're not depicted in Figures 1-13. Islets vary greatly in size; ~70% are in the size range of 50-250 μm in diameter in humans with an average in the range of 100-150 μm. Smaller islets are dispersed throughout the acinar lobules and larger islets lie along the main and interlobular ducts of the pancreas. Most islets are spherical or ellipsoid, but they can be irregular in shape sometimes reflecting the pressure of an adjacent structure, often a duct, or limitation by a tissue Flat. Several reports provide support for the presence of a higher population density of islets in the tail of the pancreas than in the head and body although others find no difference in adult humans the number of islets is calculated to be 500,000-1 million whereas there are far fewer in smaller animals. Islets included 1-2% of the pancreas in adults of most mammalian species. In addition to the islets, isolated islet cells may be found dispersed in the acinar lobules or in association with ducts **(Columbia University Irving Medical Center, 1999-2022)**

The function of the endocrine pancreas is provided by the islets of *Langerhans*. These islands dispersed within the exocrine pancreas, are made up of 4 cell types involved in the secretion of hormone into the bloodstream.

α cells and β cells regulate glucose metabolism through the production of glucagon and insulin respectively somatostatin produced by cells δ allows contraction of the gallbladder, increases intestinal mobility and inhibits the secretion of insulin and glucagon. The pancreatic polypeptide produced by PP cells regulates Secretory properties of other cell types present in the pancreas **(Bouberka, Sarah et *al*, 2021)**.

I/4.1.1. The main endocrine hormones:

Glucagon and insulin maintain blood sugar homeostasis and are used to treat hypoglycemia and hyperglycemia, respectively, in diabetic patients **(RYAD, BOUABDALLAH et *al*, 2020)**.

- **L'insuline :** Insulin is a hormone produced by the pancreas, essential for the penetration of the blood glucose in the cells. When it is lacking, the sugar level increases in the blood or the body is very sensitive to these variations: the chronicity of hyperglycemia is responsible for long-term complications affecting many organs including the eyes, kidneys, nerves, heart and vessels **(Ahlem, Chiheb, 2020).**

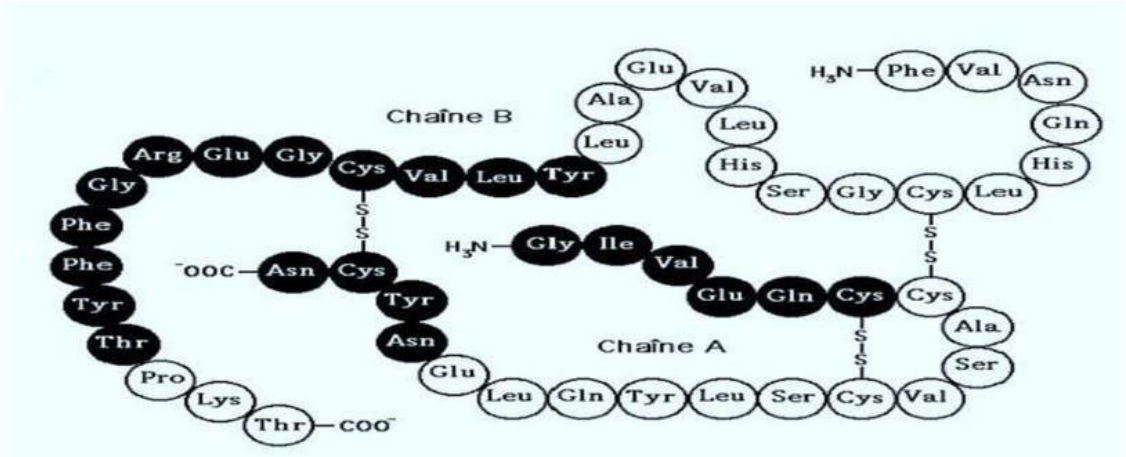


Figure 04 : The molecular structure of insulin **(Rick-Léonid Ngoua Meye Misso, 2014)**

ALA : Alanine ; ARG : Arginine ; ASN : Asparagine ; ASP : Acide Aspartique ; CYS : Cystéine ; GLN : Glutamine ; GLP : acide glutamique ; GLy : Glycine ; HIS : Histidine ; ILE : Isoleucine ; LYS : Lysine ; MET : Méthionine ; PHE : Phénylalanine ; PRO : Proline ; SER : Sérine ; THR : Thréonine ; TRP : Tryptophane ; TYR : Tyrosine ; VAL : Valine.

- **Glucagon:** Its major physiological effect is to increase plasma glucose levels as a catabolic hormone by stimulating the synthesis of hepatic glucose via the gluconeogenesis. Glucagon secretion is activated by hypoglycemia but inhibited by Hyperglycemic conditions **(Leung, P, S et *al*, 2010).**

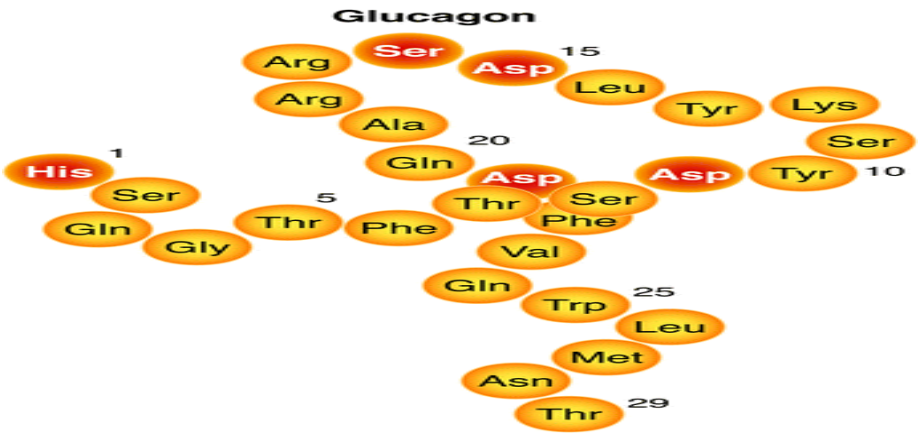


Figure 05: the molecular structure of glucagon **(Unson, C, G, 2007)**

I/4.1.3. Insulin:

I/4.1.3.1. Structure of insulin:

Insulin binds to specific receptors ***(GLUTs)*** whose number and affinity depend on the circulating insulin levels (down regulation). The binding of insulin to these receptors allows intracellular penetration of glucose and amino acids. However, penetration is free at the liver and brain. Basically, insulin reduces blood glucose concentrations, amino acids and free fatty acids. At the same time, it enriches the cellular content with glycogen, proteins and lipids. This is why insulin is the anabolic hormone par excellence **(Doumbia et *al*, 2019).**

I/4.1.3.2. Insulin biosynthesis:

Pre-pro-insulin, the precursor to insulin, is synthesized at the ribosomes, and then cleaved to pro- insulin in the endoplasmic reticulum of ß cells. This is then transported to the Golgi devices where it is stored in secretory vesicles. Pro-insulin undergoes a final cleavage in the level of these vesicles to give rise to pancreatic effluent equimolar of insulin and C-peptide **(Doumbia et *al*, 2019).**

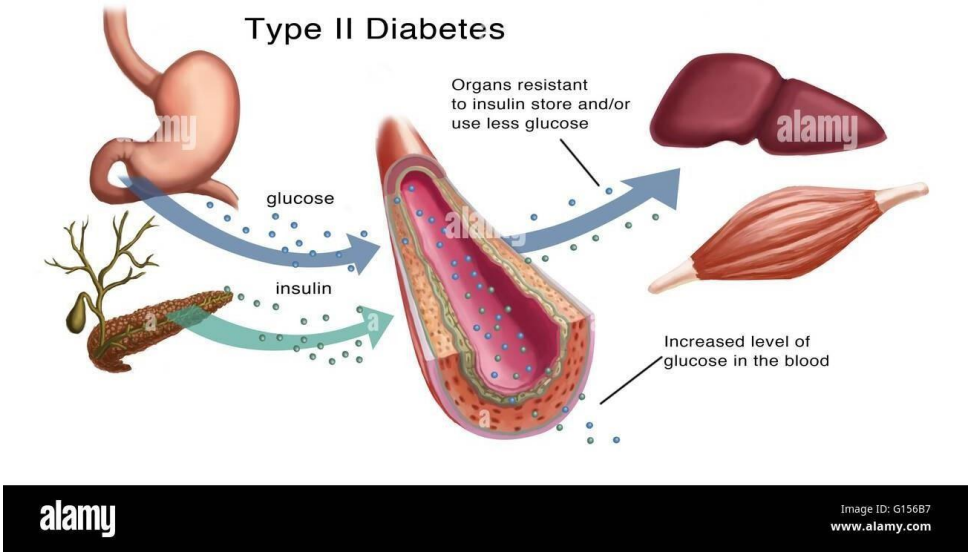


Figure 06 : Illustration of insulin and glucose production in type 2 diabetes **(Spencer Sutton.)**

I/4.1.3.3. Insulin secretion:

B or β cells make up about 60% of cells and are responsible fo insulin secretion; They are usually located in the center of the islets. A or α cells (20%) secrete glucagon. D or δ cells (10%) synthesize somatostatin. Finally PP cells (10%) are responsible for secreting pancreatic polypeptide. Within islets, paracrine communication exists and modulates the activity of the different endocrine cells **(Bessaguet, Flavien et *al*, 2021)**.

Insulin secretion is regulated in a complex way by factors metabolic, hormonal, nervous and electrophysiological.

Insulin secretion is physiologically pulsatile, with slow oscillations (every 2 hours) or fast (every 5-15 minutes). This is a property intrinsic to the cell, probably dependent on the

biological clock, this last being potentially altered during diabetes. The kinetics of Insulin discharge has two phases. The first phase starts less one minute after ingesting glucose and releases insulin already stored in the secretion granules whose purpose is to inhibit hepatic glucose production. The second occurs after one minute, but is only highlighted after 10 Minutes. It lasts about 60 minutes and allows you to drop a mixture of stored and newly synthesized insulin **(Mosbah, H et *al*, 2012).**

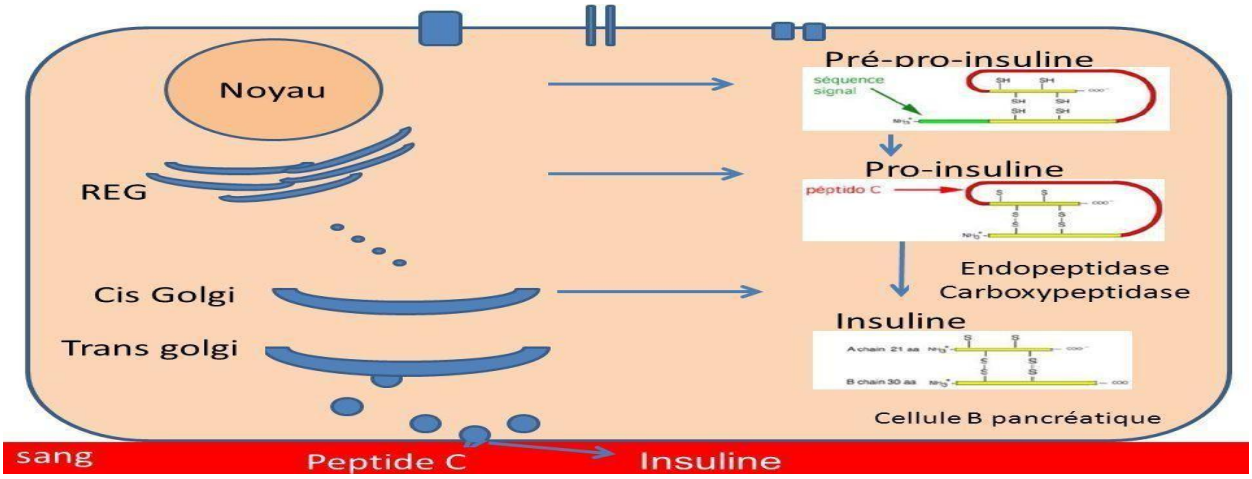


Figure 07: Production and secretion of insulin by pancreas b-cell **(C, Megan et *al*, 2005)**.

I/4.1.3.4. Insulin signaling:

The insulin signal borrows multiple pathways in the cell interconnected to each other, accounting for the pleiotropy and specificity of the signal that will concern not only energy metabolism, but also cell growth and differentiation. In pathological situations of insulin resistance, adipose tissue plays an important role due to the action of adipocytokines and the free fatty acids it secretes, which will block the transmission of the signal at different points, especially at the level of IRS proteins playing a central role in activation, but also in the inhibition of hormonal signals **(Capeau, Jacqueline, 2003).**

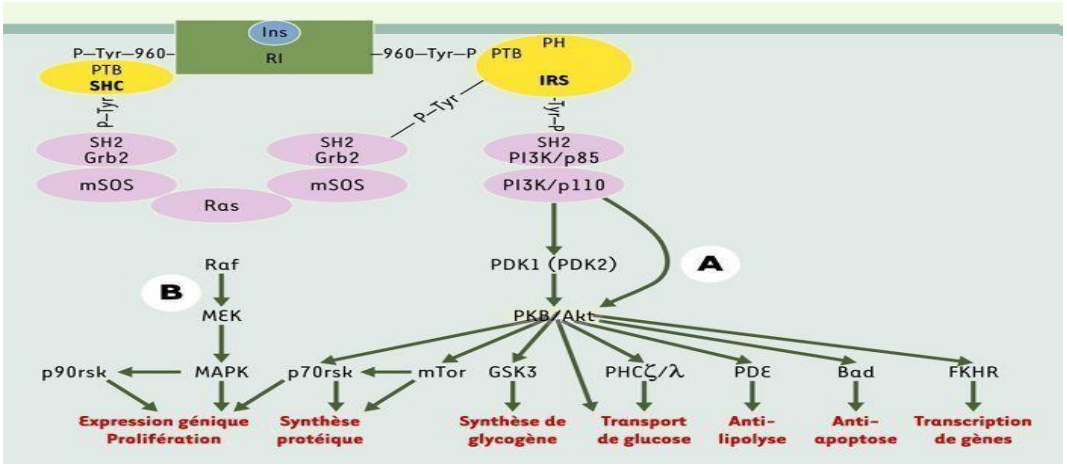


Figure 08: Insulin signaling pathways **(**PI3 kinase and MAP kinase pathways) **(Capeau, Jacqueline, 2003).**

I/4.1.3.4. 1Main insulin signaling pathways: PI3 kinase and MAP kinase:

IRS proteins (insulin receptor substrate) (yellow) are positioned at the cytosolic face of the plasma membrane by their PH domain (domain of homology with pleckstrin) which probably recognizes membrane phospholipids. They thus position their PTB domain (phosphotyrosine binding), adjacent to the PH domain, opposite the insulin receptor (RI) tyrosine 960 (in green), and bind to the RI on phosphorylated tyrosine 960 via their PTB domain (Figure 2). IRS2 will also interact with the tyrosine kinase domain of RI. The carboxy-terminal half of the IRS proteins is then close to the receptor tyrosine kinase domain, which phosphorylates specific tyrosine residues on the IRS. The phosphorylated IRS proteins are in turn recognized by the SH2 (src homology 2) domains of relay proteins (violet), the main ones being the regulatory subunit of phosphatidyl-inositol 3 (PI3) kinase, the adaptor proteins Grb2 (growth factor receptor-bound protein 2) and CrkII, the tyrosine kinase Fyn and the phosphotyrosine phosphatase SHP2 (SH2 domain protein tyrosine phosphatase-2). Has. PI3 kinase is one of the important proteins activated by this binding of IRS1 and 2; it phosphorylates membrane phosphoinositides at position 3, thus creating recognition sites for other cellular kinases such as protein kinase B (PKB)/Akt or PDK1/2 (3-phosphoinositide-dependent protein kinase 1/2). PKB activated by phosphorylation will in turn phosphorylate and activate other intracellular relays primarily involved in the metabolic effects of the hormone. Phosphorylation of glycogen synthase 3 kinase (GSK3)-β promotes glycogen synthesis. That of the p70rsk kinase and factor 4E-BP1 (4E binding protein 1), via the mTOR kinase (mammalian target of rapamycin), participates in the action of insulin on protein synthesis by increasing the general level of translation. The PI3 kinase/PKB pathway is also involved in the negative control of gene expression: by phosphorylating transcription factors of the Forkhead family, such as FKHR, it allows their retention in the cytosol and prevents them from activating, at the nuclear level, their target genes such as that of the key enzyme of gluconeogenesis, phosphoenolpyruvate carboxykinase. Also via the PKB pathway, insulin exerts an anti-apoptotic effect by phosphorylating and inhibiting pro-apoptotic factor Bad. B. From the insulin receptor, two pathways lead to the activation of the MAP kinase pathway: via IRS proteins, binding the Grb2 adapter to specific phosphotyrosines activates the nucleotide exchange factor SOS (son of sevenless) which activates the small G Ras protein in the plasma membrane by stimulating the exchange of GDP against GTP. Ras activates the RAF kinase, which then phosphorylates and activates the MAP kinase ERK1 and 2 (extracellular signal-regulated kinase). These will activate the p90rsk kinase involved in protein synthesis and will enter the nucleus in order to phosphorylate and activate transcription factors such as p62TCF involved in cell proliferation and differentiation. A second possibility of starting the MAP kinase pathway (left in the figure) starts from the insulin receptor that recruits on tyrosine 960 the adaptor proteins of the SHC family (src homologous and collagen protein) (in yellow), themselves recognized by the Grb2 protein activating the Ras pathway **(Capeau, Jacqueline, 2003).**

I/4.1.3.5. Action of insulin :

Insulin is secreted by the β cells of the pancreas directly into the portal vein the arterial insulin concentration after an overnight fast varies between 5 and 15 mU/ml in the normal individual. Insulinemia in the portal vein is about three times higher than in arterial blood because 50% of insulin is broken down as it passes through the liver. The peripheral organs are therefore exposed to much lower insulin concentrations than the liver. This should be kept

in mind when discussing the physiological actions of insulin. Another aspect that must be taken into account when considering the effects of insulin on a given organ is whether or not insulin needs to pass through a layer of endothelial cells. Some organs such as the liver, or certain regions of the brain such as the hypothalamus, are not protected by a layer of endothelial cells and insulin therefore has direct access to hepatocytes or cells of the hypothalamus. On the other hand, most other tissues are surrounded by a layer of endothelial cells that insulin must pass through before reaching its target cells. This probably explains the slower kinetics of insulin's effects on tissues, such as muscle and adipose tissue, compared to rapid effects on the liver **(Girard, J, 2008).**

I/4.1.3.5.1 Insulin and glucose metabolism:

One of the major effects of insulin is the inhibition of hepatic glucose production. The liver is very sensitive to an increase in insulinemia (doubling portal insulinemia reduces hepatic glucose production by 80%). Since the liver does not have an endothelial barrier, it is immediately in contact with insulin secreted in the portal vein and insulin is expected to have a very rapid direct action on inhibiting glucose production **(Girard, J, 2008).**

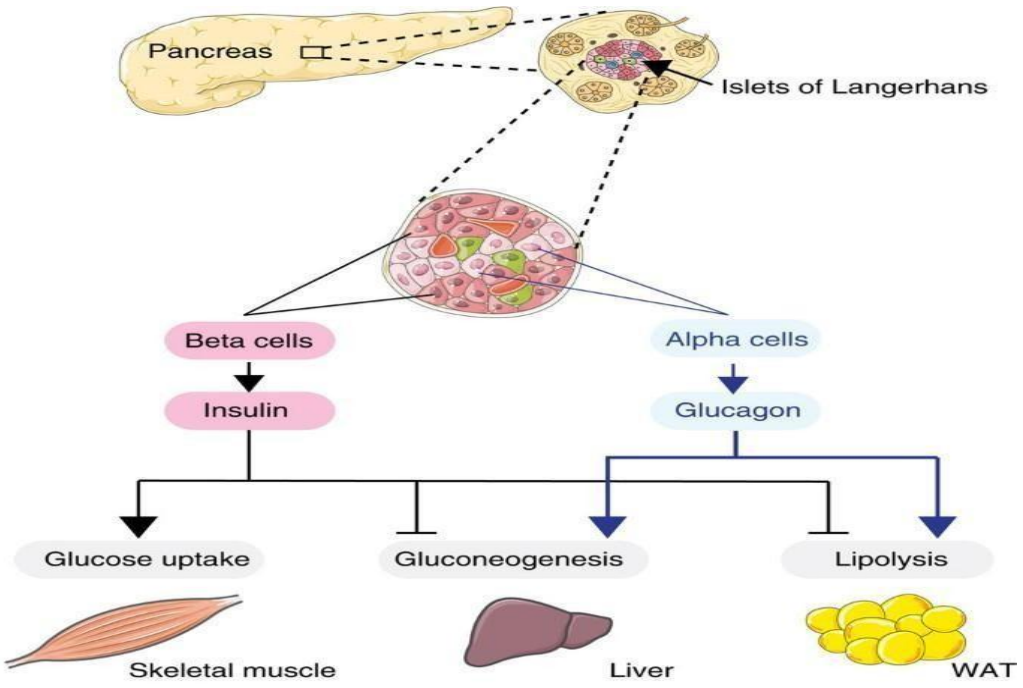


Figure 09: Pathways involved in the control of glucose homeostasis **(Ruud, J, et *al*, 2017)**

I/4.1.3.5.2 Insulin and fatty acid metabolism:

Insulin also plays a crucial role in the metabolism of fatty acids, their storage as triglycerides and their use. The physiological effects of insulin are to facilitate the storage of fatty acids in the form of triglycerides in adipose tissue and to inhibit the mobilization of triglycerides (lipolysis) of the same tissue. At low concentrations, insulin is an antilipolytic hormone **(Girard, J, 2008).**

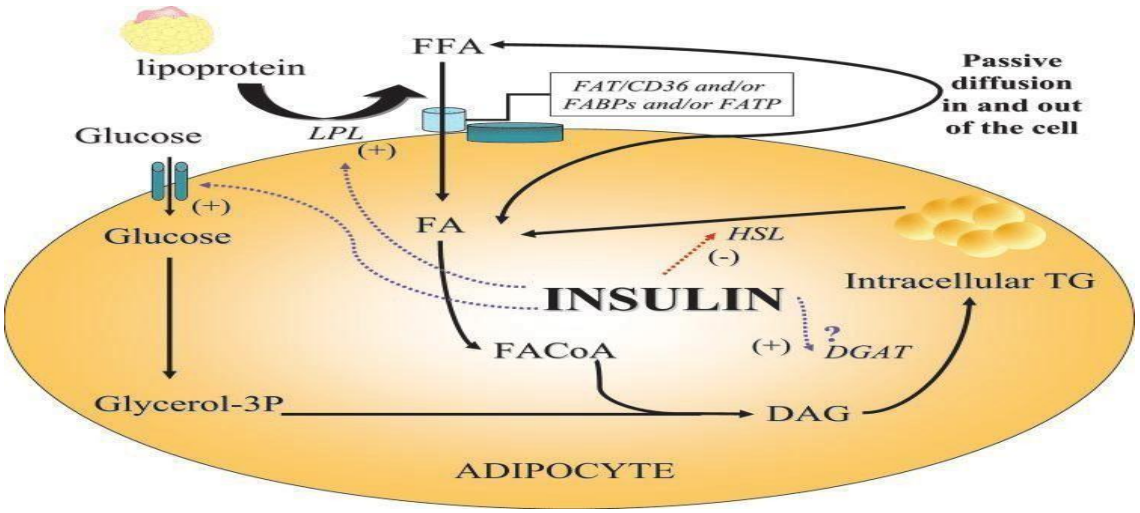


Figure 10 : role of insulin in the stimulation of adipose tissue fatty acid uptake, esterification, and storage **(Lewis, Gary et *al*, 2002)**

I/4.1.3.5.3 Insulin and protein metabolism:

One of the fundamental roles of insulin is the regulation of protein metabolism. Nitrogenous urinary loss, muscle wasting and hyperaminoacidemia are known to be characteristic of insulinopenic diabetes (type 1 diabetes). Insulin controls protein metabolism at different levels [12]. Insulin inhibits protein catabolism (proteolysis), but at concentrations higher than those needed to inhibit hepatic glucose production or lipolysis **(Girard, J, 2008).**

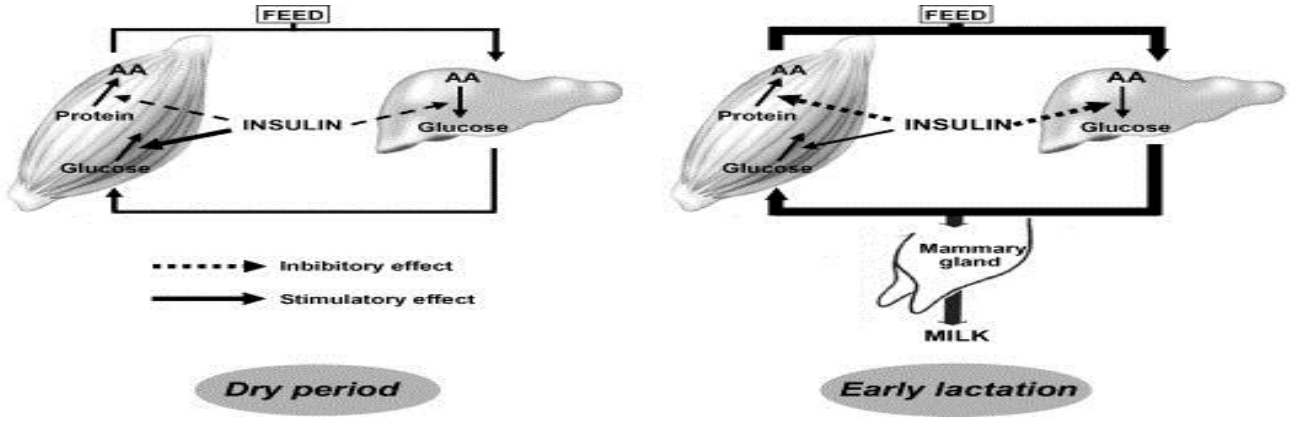


Figure 11: Regulation of protein metabolism by insulin **(Sophie Tesseraud et *al*, 2007)**

I/4.1.3.5.4 Insulin and the brain:

Insulin receptors are expressed in most tissues. In the central nervous system, insulin receptors are expressed mainly in the olfactory bulbs, hypothalamus and pituitary gland, but their function remains poorly understood. In a study by Ronald Kahn's group, transgenic mice whose insulin receptor gene was invalidated in the brain (neuron insulin receptor knock-out, NIRKO) were studied. The inactivation of the insulin receptor in the brain has no

consequence on brain development and neuron survival, but **NIRKO** mice develop diet-sensitive obesity: they increase their fat mass and leptin concentration, develop moderate insulin resistance, phosphatidyl increase their insulinemia and triglyceridemia. NIRKO mice also have impaired spermatogenesis and follicular maturation due to an abnormality in hypothalamic LH regulation. In another work, ***Morris White***'s group created mice whose insulin receptor substrate-2 (IRS-2) signaling factor, downstream of the insulin receptor, was invalidated. IRS-2 is involved in the cascade of post-insulin receptor events and undergoes rapid phosphorylation of tyrosines in response to insulin. Mice lacking IRS-2 have small ovaries, poor in follicles. The concentrations of LH, prolactin and sex steroids in these animals are low. Their pituitary gland is diminished and contains few gonadotropic cells. In females, an increase in food intake and the development of obesity are observed despite high concentrations of leptin. These two papers confirm the major role of insulin, in collaboration with leptin and other neuropeptides, in modulating hypothalamic appetite and reproductive control **(Bougnères, Pierre et *al*, 2001)**

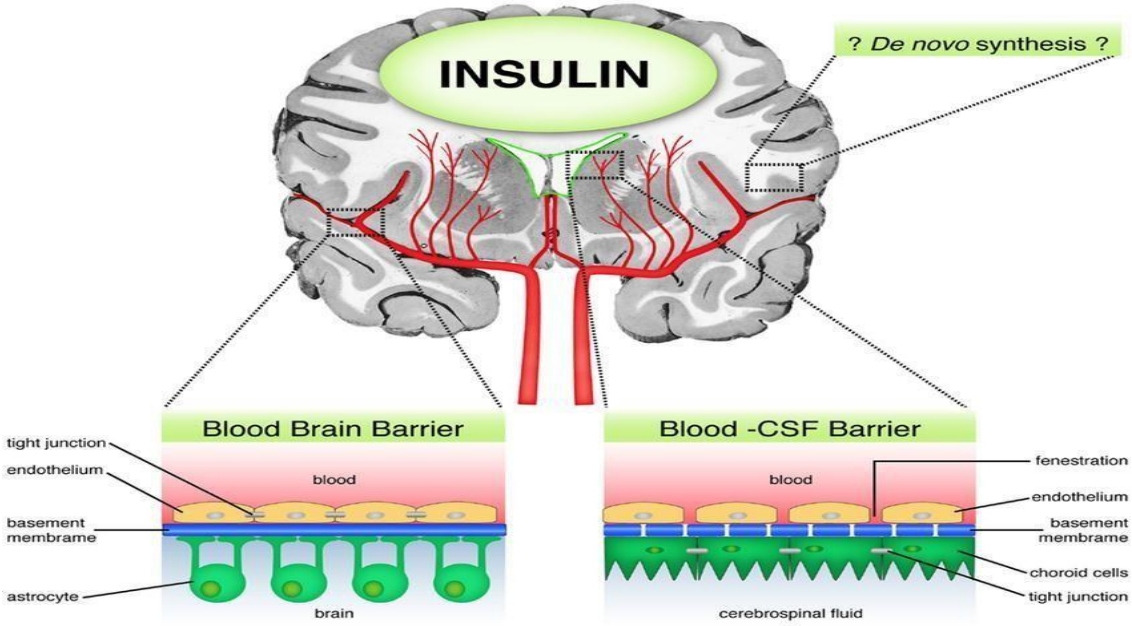


Figure 12: Sources of brain insulin. Schematic diagram showing the possible sources of brain insulin. First, peripheral insulin can access the brain through the blood brain barrier (BBB) via a selective, carrier-mediated transport system. Second, insulin may diffuse through the blood–CSF barrier in circumventricular regions, which are lacking in BBB. Third, there is some limited evidence suggesting the possibility of de novo insulin synthesis in the brain **(Abimbola A, Akintola, 2015)**

I/4.1.3.5.5 Action of insulin on the liver:

Decreased release of glucose from the liver.insulin regulates hepatic production of glucose by multiple mecanismes. Direct binding of insulin to its liver receptor, resulting in a rapid reduction in glycogenolysis.

In addition, insulin can indirectly suppress hepatic glucose production by several means, including reduction of free fatty acids circulating and glycerol due to inhibition of lipolysis, suppression of glucagon secretion **(TOUATI, Rachida, et *al*, 2021).**

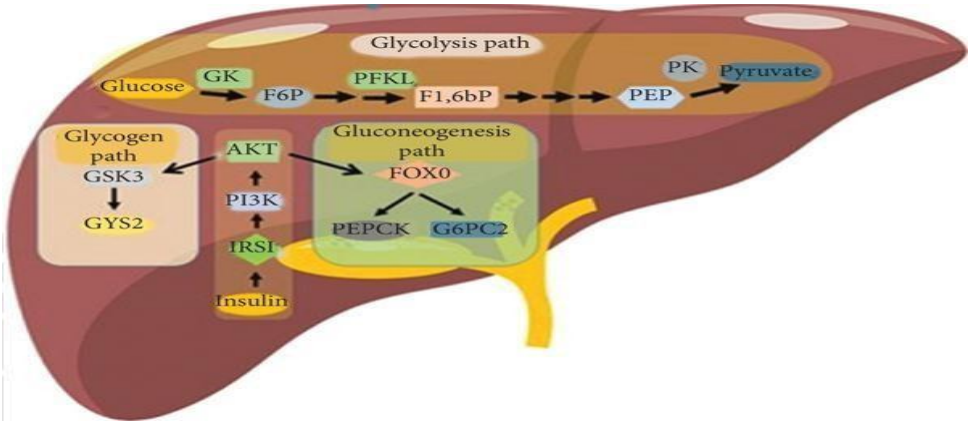


Figure 13 : Measurement. Insulin-related and glycolysis pathways. IRS1/2, insulin receptor substrate 1 ; PI3K, phosphoinositide-3 kinase ; AKT, protein kinase B ; GSK3, glycogen synthase kinase 3 ; GYS2, glycogen synthase 2 ; FOXO1, forkhead box protein O1 ; G6PC2, glucose-6-phosphatase 2 ; PEPCK, phosphoenolpyruvate carboxykinase. GK, glucokinase ; F6P, fructose 6-phosphate ; PFKL, phosphofructokinase, liver type ; F16BP, fructose 1,6-bisphosphate ; PK, pyruvate kinase **(Milad Abdollahi et *al*, 2022)**

I/5 Diabetes type 2 :

It corresponds to the old terminology of non-insulin-dependent diabetes **(L'ADA, E, T, L, O, M, S, 1999)**. Is a heterogeneous disease where genetic defects in the effect and secretion of insulin in connection with acquired factors cause a deterioration of glucose homeostasis as well as fat and amino acid metabolism, 85-90% of diabetic patients have type 2 diabetes **(Adouane Kenza et *al*, 2021)**

I/5.1. Risk factors for type 2 diabetes :

T2DM is a complex and multifactorial disease, resulting from the interaction of modifiable and non-modifiable factors:

I/5.1.1. Modifiable risk factors :

Several risk factors for developing type 2 diabetes are currently identified. The interaction between some of these endogenous, biological factors and/or exogenous (environmental factors), only accelerates predisposition of individuals.

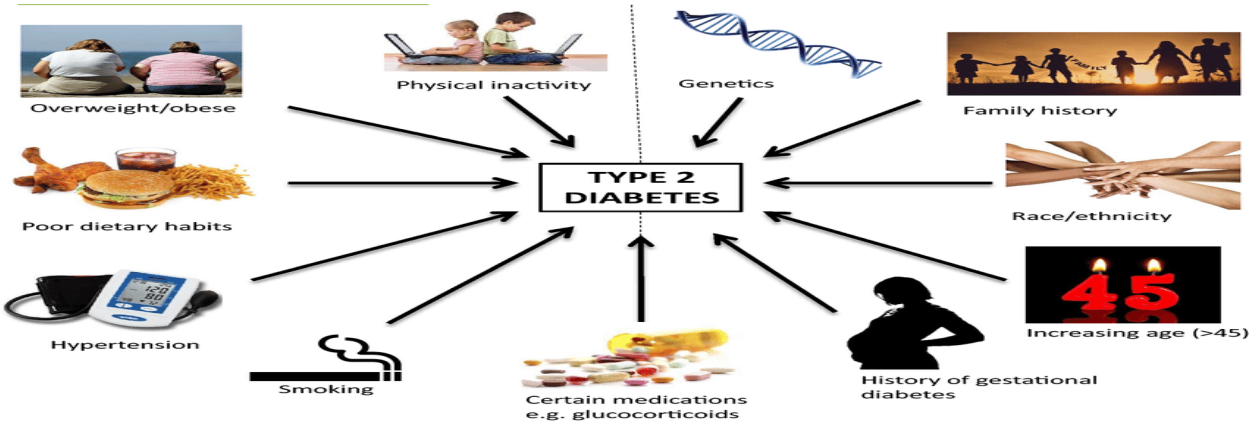


Figure 14 : Modifiable and non-modifiable risk factors of Type 2 Diabetes Mellitus **(Lankatillake, Chintha et *al*, 2019)**

I/5.1.1.1. Age :

The majority of patients are between 55 and 75 years old: beyond that, the prevalence drops due to the excess mortality associated with the disease. The increase in life expectancy plays a role in the diabetes epidemic, but its recent appearance in children. In cases of obesity, systematic oral hyperglycemia (OPGH) reveals glucose intolerance in 25% of children, and type 2 diabetes in 4% of adolescents **(Rigalleau, V et *al*, 2007)**

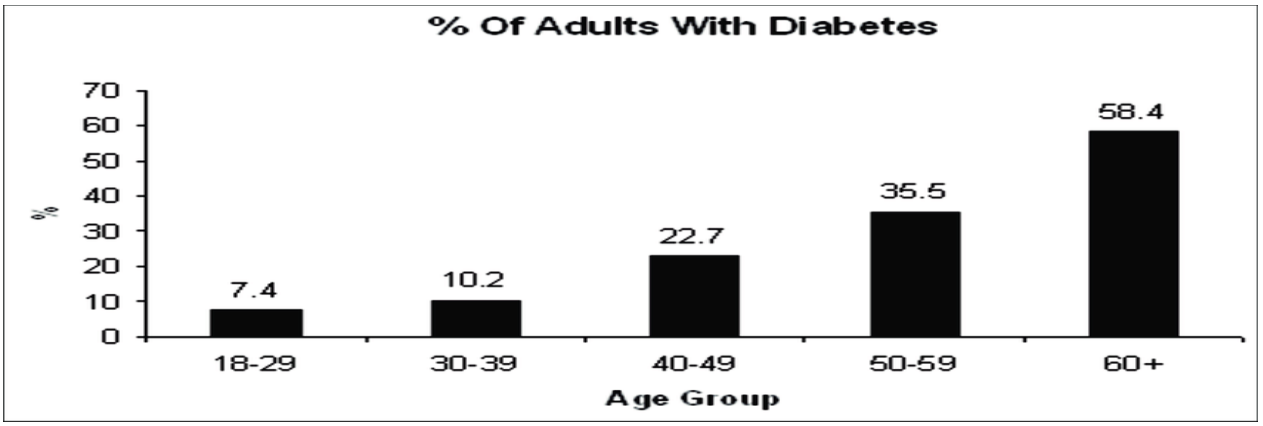


Figure 15 : percentage of adults with type 2 diabetes by age group **(Pylypchuk, George et *al*, 2008)**

I/5.1.1.2. Obesity :

Obesity is defined by the World Health Organization by a body mass index greater than 30 kg/m2; subjects with a BMI between 25 and 29.9 being classified as overweight. It is estimated that more than one billion adults are overweight, including 300 million obese **(Gremeaux, V et *al*, 2012)**

Overweight and obesity with a sedentary lifestyle, are considered responsible for the largest share of the global diabetes-related disease burden **(mondiale de la Santé, Organisation, 2016)**.Obesity is defined as an excessive increase in the body's fat mass in such a proportion that it can have an influence on the state of health **(Boirie, Y, 2009).** It is an epidemic disease associated with many cardiovascular risk factors such as diabetes, especially abdominal adiposity, is by far the most important factor for the development of type 2 diabetes **(SOUHILA, ZAHRAOUI et *al*)**.Therefore plays a major role through insulin resistance which increases the risk of DNIDs **(Gremeaux, V et *al*, 2012)**

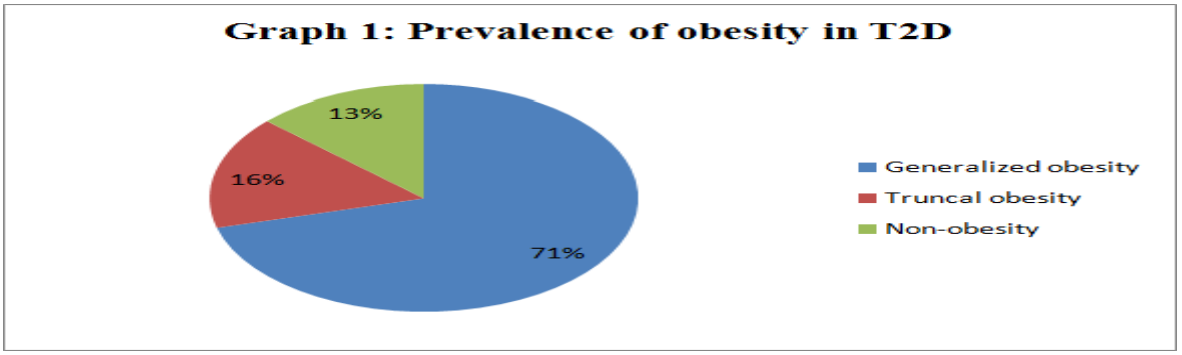


Figure 16 : prevalence of obesity in T2D **(Prabha A et *al*, 2018)**

I/5.1.1.3. Metabolic syndrome :

The increase in abdominal perimeter is one of the elements of metabolic syndrome, also characterized by frequent insulin resistance, which represents a precursor stage of T2DM **(Gremeaux, V et *al*, 2012)**. Metabolic syndrome is characterized by a constellation of physiological and biochemical abnormalities, asymptomatic, which can coexist with genetic and acquired factors **(Junquero, Didier et al, 2005)**. The metabolic syndrome is an entity that groups together in the same individual several metabolic abnormalities that each predispose to cardiovascular risk (CV). Namely a hypertriglyceridemia, low HDL cholesterol, high fasting blood glucose and central obesity according to the IDF **(Salma, M, O, U, I,C,I et *al*, 2020)**

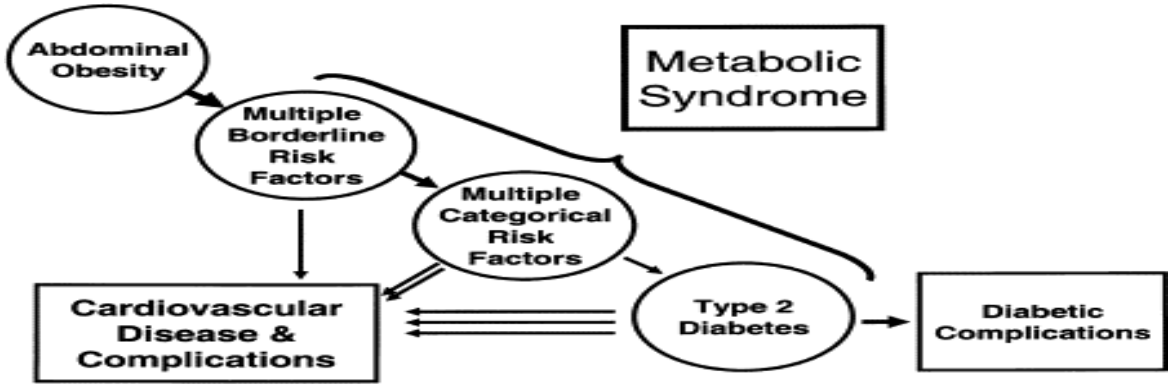


Figure 17 : Progression and outcomes of the metabolic syndrome. The metabolic syndrome arises largely out of abdominal obesity. With aging and increasing obesity, metabolic risk factors worsen. Many persons with the metabolic syndrome eventually develop type 2 diabetes. As the syndrome advances, risk for cardiovascular disease and its complications increase. Once diabetes develops, diabetic complications other than cardiovascular disease often develop. The metabolic syndrome encompasses each stage in the development of risk factors and type 2 diabete **(Scott M et *al*, 2006)**

I/5.1.1.4. Sedentary lifestyle :

Habitual physical exercise is a protective factor of a SIDDD where sedentary lifestyle may affect the interaction between insulin and its receptor **(FOUDI, Lyes, 2017)**.

Category	Protective Factors	Predisposing Factors
Body fat	Maintaining a healthy body weight; weight loss	Excessive body fat
Nutrients	N-6 polyunsaturated fatty acids; fiber; magnesium; zinc; vitamin D; selenium	Trans fatty acids; heme iron; high glycemic index and glycemic load; high starch-to-cereal-fiber ratio
Foods and beverages	Whole grains; nuts; yogurt; green leafy vegetables; whole fruits rich in anthocyanin (e.g., blueberries, grapes, apples, pears); coffee; moderate alcohol consumption	White rice; potatoes and French fries; red/processed meat; sugar-sweetened beverages; fruit juices
Dietary patterns	Adherence to healthy eating recommendations	Western dietary pattern
Physical activity	Moderate- to high-intensity exercise; brisk walking	Sedentary behavior (prolonged TV viewing, sitting)
Smoking	Smoking cessation	Active and passive smoking
Sleep	6–8 h/d of sleep	Long and short sleep durations; extended periods of rotation night shift work

Figure 18 : Role of Lifestyle Factors in Type 2 Diabetes Risk : The Nurses' Health Studies, United States, 1976-2016 **(Ley, Sylvia et *al*, 2016)**

On the other hand, physical activity in the type 2 diabetic patient allows improvement of maximum oxygen consumption (VO2 max).

The contribution of low-level physical activity in the development of type 2 diabetes is known for several years. The five interventional prospective studies currently available confirmed previous association studies published in the early nineties, and particularly the major role of regular physical exercise to prevent type 2 diabetes in high risk individuals. Its beneficial effect is sustained long time after the end of the intervention period. Data from Pimas living in Mexico compared with those living in Arizona suggest that physical activity is associated with a lower prevalence of type 2 diabetes in this genetically predisposed population **(Duclos, M et *al*, 2010)**

I/5.1.1.5. Pregnancy / gestational diabetes :

The incidence of DG is increasing worldwide. The global prevalence of gestational hyperglycemia has been estimated to be 16.9% (21.4 million live births in 2013) by criteria of the World Health Organization **(Feig, Denice S, et *al*, 2018)**

Women at high risk for GDM due to risk factors should receive nutritional advice on healthy eating and preventing excessive gestational weight gain in early pregnancy, ideally before the 15th week of pregnancy, to reduce the risk of GDM **(Feig, Denice S, et *al*, 2018)**

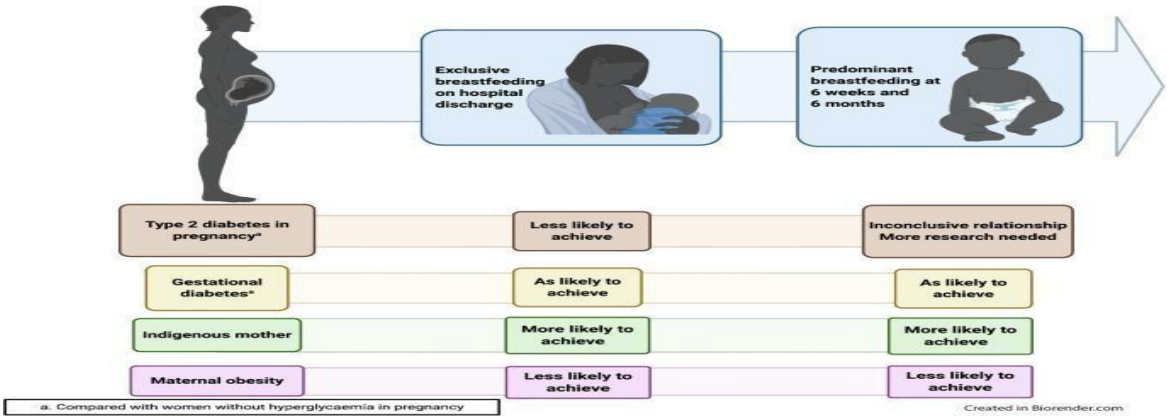


Figure 19 : Associations of gestational diabetes and type 2 diabetes during pregnancy with breastfeeding at hospital discharge and up to 6 months: the PANDORA study **(Longmore, D,K et *al*, 2020)**

I/5.1.1.6. Smoking :

Smoking increases the risk of developing type 2 diabetes by about 44%. This effect is partly linked to the increase in abdominal obesity observed in smokers. Nicotine also appears to exert a direct toxic effect on the pancreas and receptors. Insulin and induces hyperglycemia and insulin resistance. In addition, smoking induces inflammation chronic that can also contribute to the development of diabetes. Finally, as observed for the weight problem, smokers accumulate unhealthy lifestyle habits and these increase the risk of developing diabetes **(Clair, Carole et *al*, 2011)**

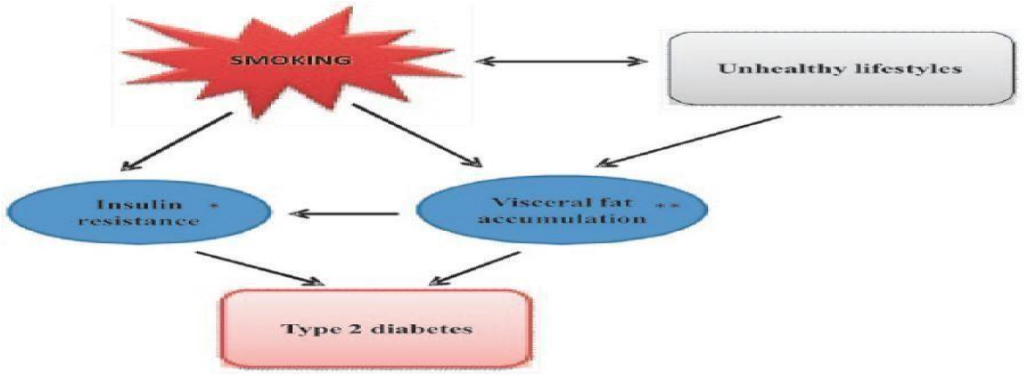


Figure 20: The impact of smoking on the development of diabetes and its complications **(1, Śliwińska-Mossoń M et *al*, 2017)**

I/5.1.1.7. Feeding :

The dietary factors most implicated in the genesis of diabetes are the high consumption of saturated fatty acids, foods with a high glycemic index and a low consumption of whole grain products **(KLAA, Fatma et *al*, 2022)**

Glycemic excursions remain limited in healthy subjects, but the degradation of postprandial glycemic control is a first step towards glucose intolerance that increases the risk of later developing type 2 diabetes **(Vors, C, et *al*, 2014)**

I/5.1.1.8. Sleep :

The consensus conference of the International Diabetes Federation (IDF) in 2007 recognized the association between type 2 diabetes and OSA based on the results of several studies that estimate that more than 40% of patients with OSA will eventually develop type 2 diabetes. The prevalence of OSA in patients with type 2 diabetes is in the order of 23%.17 this association is more pronounced in diabetic patients with damage to the autonomic nervous system **(Hernandez, Angela et *al*, 2012)**

I/5.1.1.9. Hormones and medication :

Several endocrinopathies can be linked to diabetes: hypercholesterolemia and hyperthyroidism. Also taking certain medications such as contraceptive pills, corticosteroids and diuretics **(NARIMENE, BOUHAIK et *al*, 2021)**.

I/5.1.2. Non-modifiable factors :

I/5.1.2.1. Genetic risk factors :

Genetic risk factors are assessed by a positive family history and belonging to a high-risk ethnic group including Pima Indians, African Americans, Hispanics and Pacific Asians **(Ganamé, Yaya, 2019)**

Studies conducted on twins have been of great interest in provingrole of genetic factors. Indeed the probability that the two twins are with type 2 diabetes was at least twice as high for monozygotic twins (identical twins) versus dizygotic twins (false twins). The concordance is 90%. The risk of becoming oneself diabetic, if one of the parents is type 2 diabetic, is about

40%. This frequency varies within different ethnic groups living in a identical socio-geographical environment **(Ganamé, Yaya, 2019)**

I/5.2. Physiology of type 2 diabetes :

"Common" type 2 diabetes mellitus is a multifactorial disease. Hyperglycemia is related to a decrease in glucose peripheral uptake, and to an increase in hepatic glucose production, due to reduced insulin secretion and insulin sensitivity. Multiple insulin secretory defects are present, including loss of basal pulsatility, lack of early phase of insulin secretion after intravenous glucose administration, decreased basal and stimulated plasma insulin concentrations, excess in prohormone secretion, and progressive decrease in insulin secretory capacity with time. These genetically determined abnormalities appear early in the course of the disease. Insulin resistance affects muscle, liver, and adipose tissue. For the same plasma insulin levels, peripheral glucose uptake and hepatic glucose production suppressibility are lower in diabetic patients than in controls. It results from aging of the population and from "western" lifestyle, with progressive increase in mean body weight, due to excess in energy intake, decreased energy expenses and low physical activity level **(Guillausseau, P-J et *al*, 2003)**

The role of insulin secretion deficiency, as well as the interface between insulinopenia and insulin resistance previously unclear, is currently better understood. In subjects without a genetic predisposition to type 2 diabetes, the increase in insulin requirements resulting from insulin resistance is compensated by increased insulin secretion, which helps to maintain normal blood glucose levels. On the other hand, in subjects predisposed to type 2 diabetes, the inability of the β cell to meet the increase in needs leads to a gradual rise in blood sugar and then to frank diabetes. This coping mechanism is called insulin resistance compensation by the β cell, and it is its failure that causes type 2 diabetes. Once hyperglycemia sets in, insulin secretion declines over time due to glucotoxicity and lipotoxicity **(Guillausseau, P-J et *al*, 2003)**

I/5.2.1. Insulin-resistance :

The vast majority of patients with type 2 diabetes have some degree of resistance to the action of insulin. This resistance is exerted in the 3 main target tissues of the hormone: the liver, skeletal muscle and adipose tissue. In practice, it is manifested by an increase in hepatic glucose production (mainly from gluconeogenesis), a decrease in muscle glucose uptake capacities (which is compensated by hyperglycemia) and exaggerated lipolysis with elevated plasma free fatty acid levels **(Fery, Françoise et *al*, 2005)**

The mechanisms responsible for insulin resistance associated with obesity are multiple. Free fatty acids, whose levels are high in obesity, are known to accumulate in myocytes where they interfere with the signaling of insulin by reducing the activity of phosphatidylinositol 3-kinase (PI3-kinase), a molecule recognized as essential for intracellular penetration of glucose by translocation of GLUT4 transporters (24). Similarly in this way, liver triglyceride content is inversely correlated with hepatic insulin sensitivity (25).

In addition, a series of adipokines secreted by adipocytes in proportion to fat mass decrease the action of insulin.This is, for example, the case of TNF-α (TumorNecrosis Factor-α) and resistin **(Fery, Françoise et *al*, 2005)**

Insulin resistance affects virtually all type 2 diabetics. Detectable 10 to 20 years before

diagnosis, even in the absence of obesity, its presence predicts the subsequent occurrence of the disease in related subjects. The effects (anabolic and anticatabolic) of insulin outside carbohydrate metabolism can also be reduced, including its ability to reduce lipolysis in adipose tissue, which is important because the fatty acids released in this way contribute to disturbances of carbohydrate homeostasis. Protein metabolism has been less studied and appears less disrupted, but a defect in mitochondrial protein synthesis could play a key role in disrupting energy metabolism in these patients. The fact that insulin resistance is at least partially, reversible under the influence of hygienic measures or certain oral antidiabetics, reinforces its interest for the clinician **(Rigalleau, V et *al*, 2007)**

I/5.2.1.1. Lipotocixity :

The term „lipotoxicity" was coined by Unger to describe the deleterious effect of tissue fat accumulation on glucose metabolism. However, lipotoxicity has assumed added significance (see textbox: Lipotoxicity). Experimental **NEFA** elevation to reproduce levels in type 2 diabetes causes severe muscle/liver insulin resistance and inhibits insulin secretion, reproducing the three basic core defects of type 2 diabetes. Elevated plasma **NEFA** impairs glucose oxidation/glycogen synthesis and decrease glucose transport/phosphorylation. Most importantly, lipid infusion to increase plasma NEFA levels in participants with normal glucose tolerance caused a dose–response inhibition of insulin receptor/IRS-1 tyrosine phosphorylation and PI-kinase activity, which correlate closely with reduced insulin-stimulated glucose disposal **(DeFronzo, R, A, 2010)**

I/5.2.1.2. Inflammation :

Tnf **(a.k.a. Tnfa)** is a pro-inflammatory cytokine secreted predominantly by monocytes and macrophages and has wide ranging biological effects on lipid metabolism, coagulation and endothelial function. Activation of the Tnf receptor results in stimulation of NFjB signaling via Ikkb. An important early study on the interplay between obesity, inflammation and insulin resistance showed that Tnf expression was elevated in adipose tissue isolated from different obese rodent models. Hotamisligil et al also showed that immuno-neutralization of Tnf in obese fatty rats ameliorated insulin resistance. Subsequently, Hotamisligil et al went on to show similar correlations between TNF levels, obesity and insulin resistance in man. Corresponding in vitro experiments demonstrated that by activating Ikkb, Tnf stimulation leads to serine phosphorylation of Irs1 which attenuates its ability to transduce insulin mediated cellular events. Mice genetically deficient in Tnf or the Tnf receptor 1 gene **(Tnfr1)** do not develop insulin resistance caused by high fat feeding or obesity **(De Luca, Carl et *al*, 2008)**

Tnf can also affect insulin signaling independent of IRS1. Thus, treatment of cultured 3T3-L1 adipocytes with Tnf leads to reduced expression of the insulin receptor, IRS1 and Glut4 genes, as well as a decrease in insulin stimulated glucose uptake. Ruan et al. also showed a Tnf-induced decrease in 3T3-L1 adipocyte genes, including GLUT4, Hormone Sensitive Lipase (HSL), long-chain fatty acyl CoA synthetase, adiponectin **(ADIPOQ),** the transcription factor CCAAT/enhancer binding protein-alpha (C/EBP), and the nuclear receptors Pparg and retinoic acid x receptor (RXR). These genes all contribute to glucose homeostasis, both directly and indirectly and changes in adipocyte expression of these genes likely contribute to insulin resistance in obesity induced-chronic inflammation **(De Luca, Carl et *al*, 2008)**

I/5.2.1.3. The insulin resistance signaling pathway :

Insulin signaling involves a complex signaling cascade downstream of the insulin receptor. This signaling cascade branches into two main pathways. The first is the phosphatidylinositol 3-kinase **(PI3K)**-AKT (also called protein kinase B **(PKB))** pathway which is largely responsible for insulin action on glucose uptake, as well as other metabolic actions of insulin, including the suppression of gluconeogenesis. The second pathway is the Ras-mitogen activated protein kinase **(MAPK)** pathway which mediates gene expression, but also interacts with the PI3K-AKT pathway to control cell growth and differentiation. The common intermediate to these pathways is IRS, which include four distinct family members, IRS1-4. For the purpose of this review, we will focus on IRS1, as defects in insulin signaling typically involve this IRS. Activation of the insulin receptor leads to tyrosine phosphorylation of IRS1 thereby initiating signal transduction. When IRS1 is alternatively phosphorylated on serine 307, its downstream signaling ability is diminished. Serine kinases that phosphorylate serine 307 include I kappa B kinase beta **(Ikkb)** in the NFjB pathway and C-jun N-terminal kinase 1 **(Jnk1)** in the JNK/AP-1 pathway. Additional inflammation-related negative regulators of IRS proteins include the suppressor of cytokine signaling **(Socs).** Socs1 and Socs3, which are induced in inflammation, promote the ubiquitylation and subsequent degradation of IRS proteins **(De Luca, Carl et *al,* 2008)**

I/5.3. Complications of type 2 diabetes :

People with type 2 diabetes are at increased risk of many complications, which are mainly due to complex and interconnected mechanisms such as hyperglycemia, insulino-resistance, low-grade inflammation and accelerated atherogenesis:

I/5.3.1. Micro-ongiopathic :

I/5.3.1.1. Diabetic retinopathy :

Retinopathy which is paradoxically slightly progressive must however be screened and treated in these rather old patients which are globally at high ophthalmologic risk. Diabetic retinopathy is the fourth leading cause of visual acuity loss in diabetics over the age of 65. Its precise prevalence is poorly known. According to ENTRED data, 7.9% of type 2 diabetics have treatment-related retinopathy and 3.9% have severe visual acuity in one eye. It is the consequence of chronic hyperglycemia but its evolution is also influenced by blood pressure balance and, to a lesser degree **(Schlienger, Jean-Louis, 2013)**

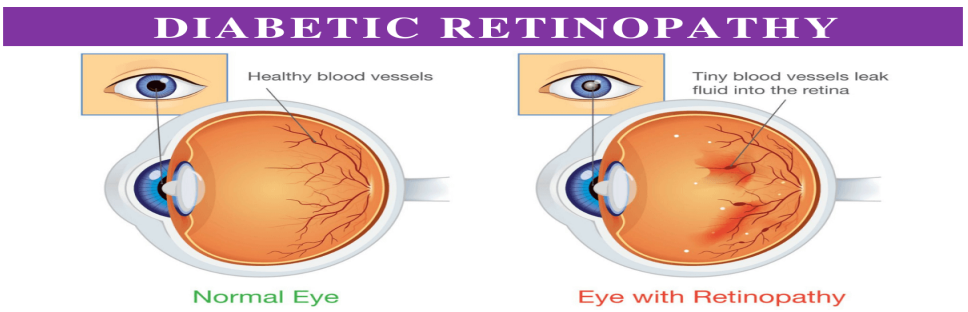


Figure 21 : The difference between a normal retina and diabetic retinopathy **(sriramakrishnahospital)**

I/5.3.1.2. Diabetic nephropathy :

Nephropathy is frequent in type 2 diabetes but has a mixed origin. Now it is the highest cause of end-stage renal disease. Better metabolic and blood pressure control and an improved management of microalbuminuria are able to slowdown the course of the disease. This complication is estimated in a variable way according to the criteria used to define it. Its prevalence would be about 50% after 65 years. As with retinopathy, hyperglycemia and the duration of diabetes progression are the two main determining factors, but there may be neuropathies without retinopathy. In fact, the pathophysiology of the neurotoxic effect of chronic hyperglycemia is complex and involves the end products of glycation, oxidative stress **(Schlienger, Jean-Louis, 2013)**

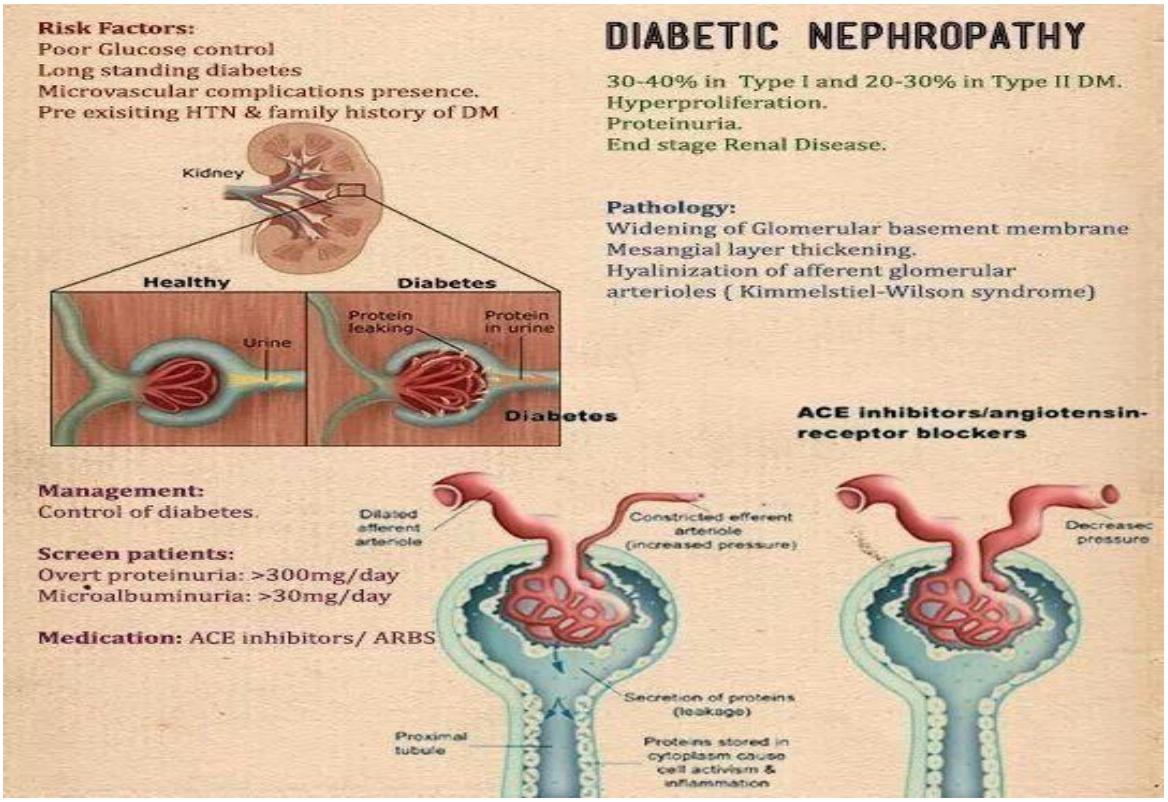


Figure 22 : The difference between a normal kidney and diabetic nephropathy **(Diabetic Nephropathy)**

I/5.3.2.Macro-ongiopathic :

Atherosclerosis is the most important complication of diabetes and diabetes is an important risk factor for cardiovascular disease. Atherosclerosis develops more rapidly and at an earlier age in diabetic patients than in non-diabetic people. Although a number of cardiovascular risk factors are more common in diabetic than non-diabetic people, these do not entirely account for the increased frequency of cardiovascular disease. The identity of the additional factor or factors which result in increased atherosclerosis in diabetes is unknown but attention should be paid to the role of glycated lipoproteins and of hyperinsulinaemia. In treating diabetic patients, attention should be paid to cardiovascular risk factors such as dyslipidaemia and hypertension as well as to the control of blood glucose **(Stout, Robert W, 1993)**

I/6 Management of type 2 diabetes :

I/6.1. Dietary hygiene measures :

The goal of treating diabetes is to control blood sugar levels and prevent hyperinsulinemia in order to prevent or delay the development of problems associated with the disease. A healthy lifestyle is also required, including regular physical activity and balanced nutrition. Medical treatment alone is insufficient.

I/6.1.1. Physical activity :

Physical activity improves glycemic control and reduces the risk of cardiovascular disease (CVD) and mortality in patients with type 2 diabetes (T2D). Moderate to vigorous physical activity is recommended to manage T2D; however, patients with T2D can be physically weak, making it difficult to engage in the recommended levels of physical activity. Daily physical activity includes various activities performed during both occupational and leisure time such as walking, gardening, and housework that type 2 diabetic patients should be able to perform without considerable physical burden. This review focuses on the association between daily physical activity and T2D. Walking was the most common form of daily physical activity, with numerous studies demonstrating its beneficial effects on reducing the risk of T2D, CVD, and mortality. Walking for at least 30 min per day was shown to reduce the risk of T2D by approximately 50%. Additionally, walking was associated with a reduction in mortality. In contrast, evidence was extremely limited regarding other daily physical activities such as gardening and housework in patients with T2D. Recent studies have suggested daily physical activity, including non-exercise activity thermogenesis, to be favorably associated with metabolic risks and mortality. However, well-designed longitudinal studies are warranted to elucidate its effects on overall health **(Hamasaki, Hidetaka, 2016)**

I/6.1.2. Nutritional management :

Dietary factors are of paramount importance in the management and prevention of type 2 diabetes. Despite progress in formulating evidence based dietary guidance, controversy and confusion remain. In this article, we examine the evidence for areas of consensus as well as ongoing uncertainty or controversy about dietary guidelines for type 2 diabetes. What is the best dietary approach? Is it possible to achieve remission of type 2 diabetes with lifestyle behaviour changes or is it inevitably a condition causing progressive health decline? We also examine the influence of nutrition transition and population specific factors in the global context and discuss future directions for effective dietary and nutritional approaches to manage type 2 diabetes and their implementation **(Forouhi, Nita G, et *al*, 2018)**

I/6.2.medication treatment :

Physical activity and diet are not enough to treat type 2 diabetes, so doctors resort to other methods of treatment.

I/6.2.1. Oral antidiabetic drugs :

Oral therapy of type 2 diabetes (T2D) is becoming increasingly complex during the last decade, with first the launch of glitazones, then that of gliptins and finally, very recently, that of gliflozins. However, the two oral glucose-lowering agents developed more than 50 years

ago, metformin and sulfonylureas, still remain the leaders in the market. After failure of metformin monotherapy, the choice of antidiabetic medications is difficult and should be made taking into account the benefit-risk balance, with a special attention to cost of therapy and a focus on a patient-centered approach. This strategy is recommended in the recently updated joint ADA-EASD position statement, in January 2015. If the main principles of T2D therapy are universal, particularities should probably be discussed regarding regional situations, and the African continent obviously presents specificities in this respect **(Scheen, A-J, 2015)**

I/6.2.1.1. Biguanids :

Metformin is an alkaloid isolated from Galega officinalis (French Lilac), a plant used in long-standing folk medicine. Its hypoglycemic activity was studied by the French diabetologist Jean Stern, who published his work in 1957. It was then developed by ARON laboratories, and marketed under the name Glucophage®. Subsequently, this pharmacological class developed and included three molecules: in addition to metformin, phenformin, and buformin **(Scheen, A-J, 2015)**

I/6.2.1.2. Glitazone :

Type 2 diabetes mellitus is a growing problem not only in the United States but also across the world. There is now strong evidence that intensive control of blood glucose can significantly reduce and retard the microvascular complications of retinopathy, nephropathy, and neuropathy. Ultimately however, up to 80% of type 2 diabetics die from macrovascular cardiovascular disease. This increased incidence of atherosclerotic disease is intricately associated with insulin resistance, which is a major pathophysiologic abnormality in type 2 diabetes. There is strong evidence that insulin resistance is involved in the development of not only hyperglycemia, but also dyslipidemia, hypertension, hypercoagulation, vasculopathy, and ultimately atherosclerotic cardiovascular disease. This cluster of metabolic abnormalities has been termed the insulin resistance or cardiovascular dysmetabolic syndrome. The thiazolidinediones (rosiglitazone and pioglitazone), a new class of oral antidiabetic agents, are “insulin sensitizers” and exert direct effects on the mechanisms of insulin resistance. These effects not only improve insulin sensitivity and glycemic control with reduced insulin requirements, but also have potentially favorable effects on other components of the cardiovascular dysmetabolic syndrome. Long-term studies are needed to determine whether the insulin-sensitizing effects of the glitazones can prevent or delay premature atherosclerotic cardiovascular disease, morbidity, and death **(Mudaliar, Sunder et *al*, 2001)**

I/6.2.1.3. Sulphonylides :

Sulfonylureas are characterized by an initially strong lowering of blood sugar and have been established in the treatment of type 2 diabetes for more than 50 years.These are new classes of PPAR agonists. They stimulate insulin secretion by binding to the Langerhans beta cell by binding to a membrane receptor which opens calcium channels and closes potassium channels **(TOUATI, Rachida, et *al*, 2021)**

I/6.2.1.4. Glunids :

Glinides therefore have a lower hypoglycemic power than insulin or sulfonamides during PA. In addition, glinides did not cause the appearance of hypoglycemia at the end of the session or

in the evening. The results suggest that there is no indication to decrease the dosage of glinides before a moderate-intensity PA session **(Duclos, M et *al*, 2010)**

I/6.2.1.5. Alpha-glucosidase inhibitors :

The development of antidiabetic drugs with complementary mechanisms of action appears more and more necessary in order to achieve durable glycaemic control in type 2 diabetes. By inhibiting in a reversible way the hydrolysis of disaccharides and the ultimate steps of the digestion of dietary polysaccharides, α-glucosidase inhibitors reduce postprandial blood glucose raise in diabetics. This therapeutic class, limited in Europe until recently to acarbose, has been enlarged with the marketing of miglitol, whose pharmacokinetic properties might lead to better long term tolerance. The improvement of glycaemic control obtained with α-glucosidase inhibitors is now better evaluated and appears similar whatever the combinations with other antidiabetic drugs, including insulin. The role of α-glucosidase inhibitors in the overall therapeutic strategy of type 2 diabetes and their benefit on the evolution of long term complications remains to be clarified **(Blicklé, J, F et *al*, 1999)**

I/6.2.2. Insulin therapy for type 2 diabetes :

Among the main reasons for hospitalization of a type 2 diabetic (T2D) is the initiation of insulin therapy for an improperly balanced T2DM on oral antidiabetic drugs. The objective of our study is to compare the profiles of inpatients with those treated on an outpatient basis and to evaluate the effectiveness of insulin therapy for each group **(Grira, W, et *al*, 2016)**

Outpatient insulin therapy seems to be an interesting alternative to conventional hospitalization; indeed the results show a comparable improvement in glycemic control without significant increase in the risk of hypoglycemia. The limitation of our study is the small number of students **(Grira, W, et *al*, 2016)**

CHAPTER II:
RELATIONSHIP BETWEEN OBESITY AND TYPE 2 DIABETES

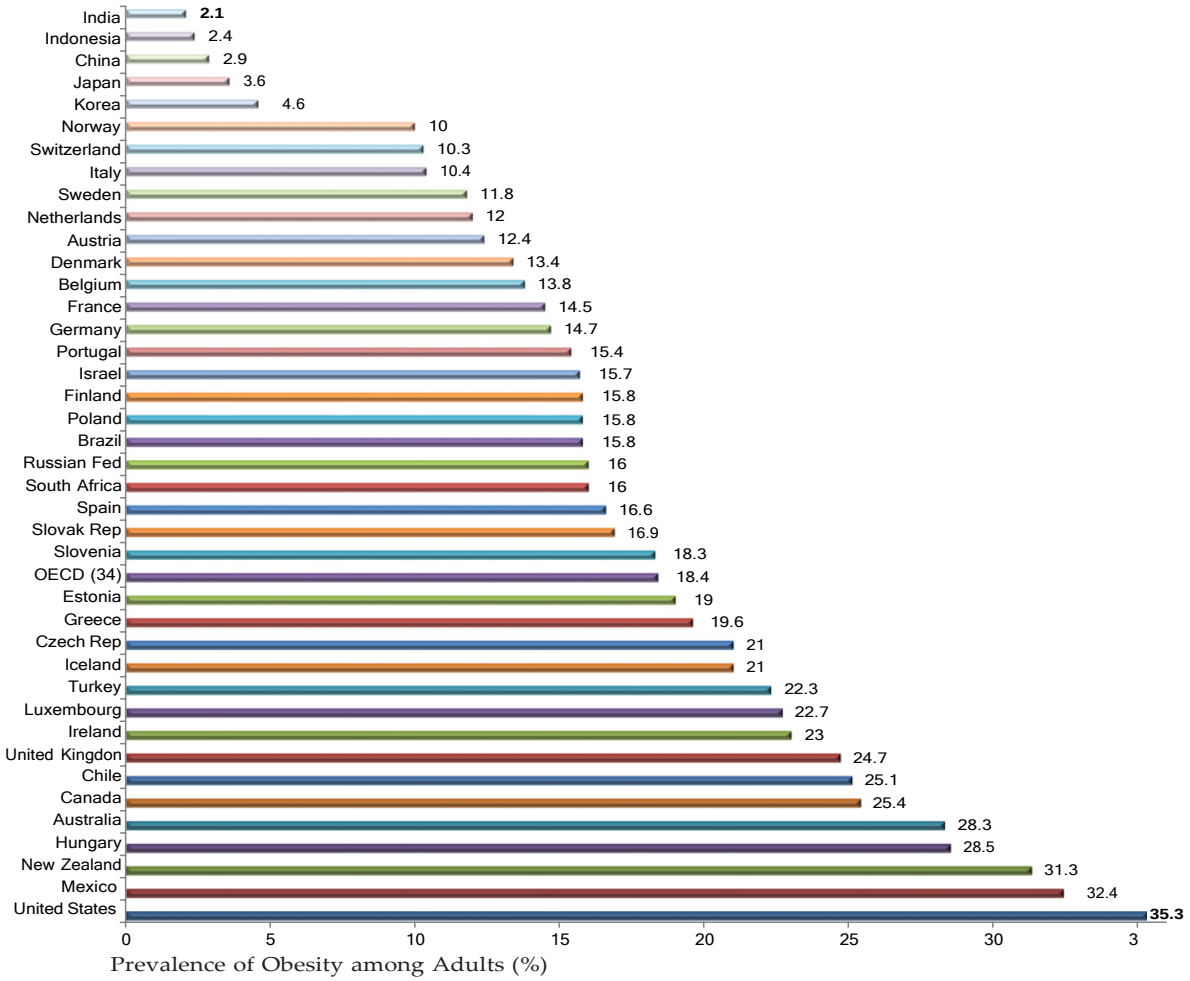
From obesity to type 2 diabetes in children and adolescents obesity has a prevalence of 15-16% among subjects aged 6-17 yr. in United States as well as in Europe? Another 10 to 15% of children and adolescents appear to be at risk of obesity. The presence of type 2 diabetes among adolescents in our country represents a challenge from both a screening and a therapeutic point of view. In addition to obesity, a positive familial history, puberty and ethnic susceptibility as well as conditions known to exhibit insulin resistance (acanthosis nigricans dislipidemia, polycystic ovary syndrome) represent majors risk factors. Detecting subjects at risk among a large number of obese children appear to be a critical step. Therapy of type 2 diabetes requires as important means as those set for type 1 diabetes, taking into account the fact that both types of diabetes share the same vascular complication **(Theintz, G, 2005)**

II/1. Definition of obesity :

The World Health Organization (WHO) in 1997 declared obesity as a major public health problem and a global epidemic. In general, a body mass index of 25 kg/m^2 or greater is considered overweight and 30 kg/m^2 or greater is considered obese. According to the estimates by WHO, more than 1.9 billion adults aged 18 years and older are overweight, and of those, over 650 million adults are obese **(Haththotuwa, Rohana N et *al*, 2020)**

II/1.1 The explosion of obesity around the world :

Worldwide, the prevalence of obesity has increased dramatically during the last four decades, and if this trend continues, a majority of the world‟s adult population will be either overweight or obese by 2030. Interaction of many factors including genetic, metabolic, behavioral, and environmental influences has resulted in this situation. The problem of obesity is a major contributor to the global burden of chronic disease and disability, with serious social and psychological implications that affect virtually all ages and socioeconomic groups **(Haththotuwa, Rohana N et *al*, 2020)**



<u>Figure 23 :</u> Share of adults that are obese, 2016 **(Evan L et *al*, 2016)**

II/2. Relationship between type 2 diabetes and obesity :

The relationship between obesity and diabetes is of such interdependence that the term „diabesity" has been coined. The passage from obesity to diabetes is made by a progressive defect in insulin secretion coupled with a progressive rise in insulin resistance.

Both insulin resistance and defective insulin secretion appear very prematurely in obese patients, and both worsen similarly towards diabetes. Thus, the classic „hyperbolic relationship" between insulin resistance and insulin secretion and the „glucose allostasis concept" remain prevailing concepts in this particular field of knowledge.

Both insulin resistance and defective insulin secretion appear very prematurely in obese patients, and both worsen similarly towards diabetes. Thus, the classic „hyperbolic relationship" between insulin resistance and insulin secretion and the „glucose allostasis

concept‟ remain prevailing concepts in this particular field of knowledge **(Golay, Alain et *al*, 2005).**

II/2.1. Definition of BMI and body fat :

- **Body mass index :** the BMI is a tool used by healthcare professionals to help estimate a person‟s risk for chronic disease. BMI uses height and weight to determine one‟s optimal health.

• If your BMI is between 20 and 22, you have the ideal amount of body fat, which is associated with living longest and the lowest incidence of illness.

• If your BMI is between 22 and 25, this is acceptable and associated with good health.

• If your BMI is between 25 and 30, you are considered overweight and should find ways to lose weight through exercise and diet.

• If your BMI is over 30, this indicates an unhealthy condition. Your weight is putting you at risk for heart disease, stroke, diabetes, high blood pressure and some cancers. You should lose weight by changing your diet and exercise behaviors **(Obese, H, J, O, R, 1998)**

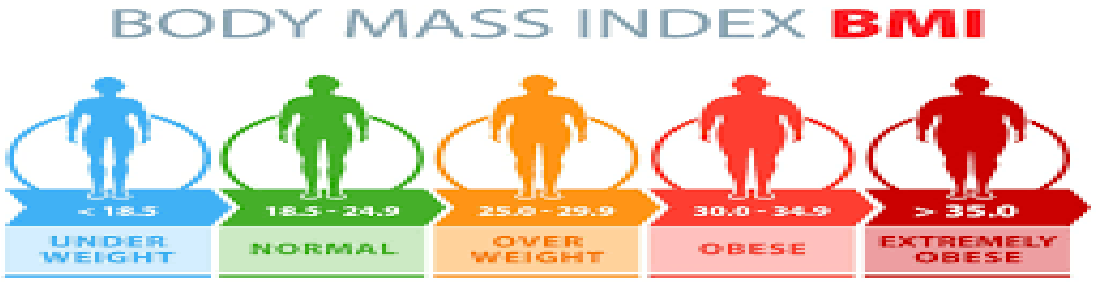


Figure 24 : body mass index according to the WHO **(https://westmedical.com/wp-content/uploads/2022/12/3932e867ae54709fb3d2b4f4ebebca7e6f8f6ff4-1993x1199-1.jpgv)**

Body fat : Also called adipose tissue is a loose connective tissue composed mainly of adipocytes. In addition to adipocytes, adipose tissue contains the stromal vascular fraction (SVF) of cells, including preadipocytes, fibroblasts, vascular endothelial cells,and a variety of immune cells (i.e. macrophages of adipose tissue (ATMs)). Adipose tissue comes from preadipocytes. Its main role is to store energy in the form of lipids, even if it repays and insulates the body. Far from being hormonally inert, adiposetissue has been recognized in recent years as a major endocrine organ, as it produces hormones such as leptin, estrogen, resistance and cytokine TNFα. In addition, adipose tissue can affect other organ systems in the body and can lead to disease. Obesity or overweight in humans and most animals does not depend on body weight, but on the amount of body fat - specific, adipose tissue. The two types of adipose tissue are whiteadipose tissue (WAT) and brown adipose tissue (BAT). The formation of adipose tissue appears to be controlled in part by the adipose gene **(https://educalingo.com/)**

II/3. Obesity and insulin resistance :

The association of obesity with type 2 diabetes has been recognized for decades, and the major basis for this link is the ability of obesity to engender insulin resistance. Insulin resistance is a fundamental aspect of the etiology of type 2 diabetes and is also linked to a

wide array of other pathophysiologic sequelae including hypertension, hyperlipidemia, atherosclerosis (i.e., the metabolic syndrome, or syndrome X), and polycystic ovarian disease. Although many details of the mechanisms by which the enlarged adipose tissue mass that defines obesity causes systemic insulin resistance remain unknown, the past several years have witnessed an explosive increase in our understanding of what may now be referred to as the adipo-insulin axis. There are also grounds for considering the related possibility that insulin resistance and hyperinsulinemia, in addition to being caused by obesity, can contribute to the development of obesity. In this Perspective, we will review recent progress, highlight areas of controversy or uncertainty, and suggest approaches to clarifying the unresolved issues **(Kahn, Barbara B et *al*, 2000)**

II/3.1. Insulin action in adipocyte :

Insulin is a critical regulator of virtually all aspects of adipocyte biology, and adipocytes are one of the most highly insulin-responsive cell types. Insulin promotes adipocyte triglyceride stores by a number of mechanisms, including fostering the differentiation of preadipocytes to adipocytes and, in mature adipocytes, stimulating glucose transport and triglyceride synthesis (lipogenesis), as well as inhibiting lipolysis (Figure 24). Insulin also increases the uptake of fatty acids derived from circulating lipoproteins by stimulating lipoprotein lipase activity in adipose tissue. Insulin‟s metabolic effects are mediated by a broad array of tissue-specific actions that involve rapid changes in protein phosphorylation and function, as well as changes in gene expression. The fundamental biologic importance of these actions of insulin is evidenced by the fact that the insulin signaling cascade which initiates these events is largely conserved in evolution from *C. elegans* to humans **(Kahn, Barbara B et *al*, 2000)**

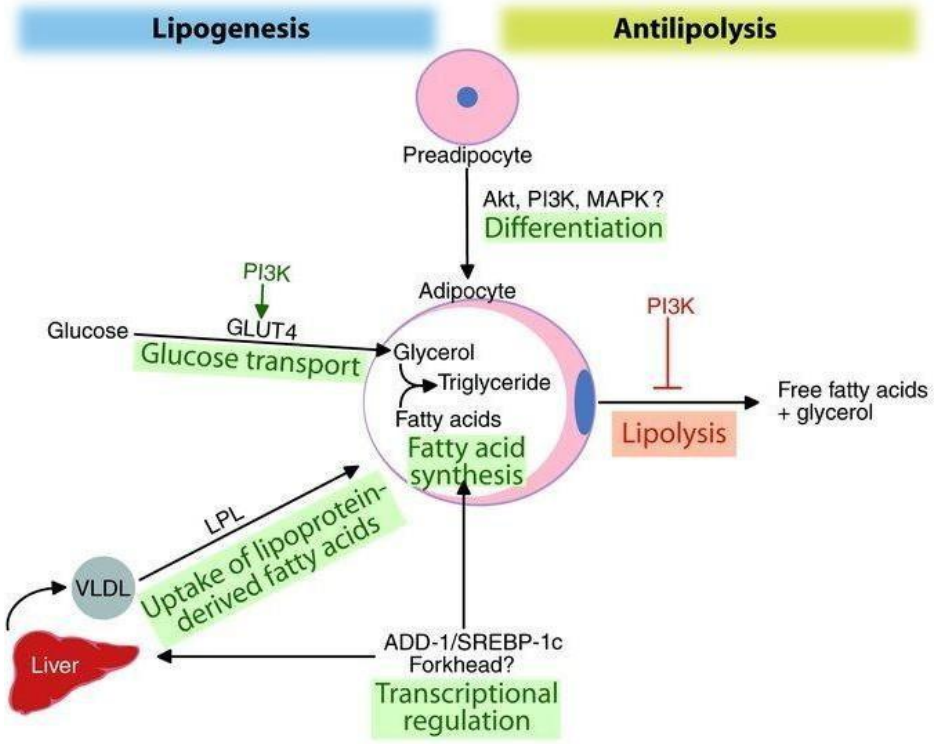


Figure 25 : Pleiotropic effects of insulin to promote adipose storage. Insulin stimulates differentiation of preadipocytes to adipocytes. In adipocytes, insulin promotes lipogenesis by stimulating the uptake of glucose and lipoprotein-derived fatty acids and by inducing ADD-

1/SREBP-1c, which regulates genes promoting fatty acid synthesis and lipogenesis, not only in adipocytes but also in hepatocytes. Insulin may also regulate transcription through Forkhead transcription factors. Insulin diminishes triglyceride breakdown by inhibiting lipolysis. Many of these metabolic pathways are regulated by the PI3K signaling pathway **(Kahn, Barbara B et *al*, 2000)**

The initial molecular signal for insulin action involves activation of the insulin receptor tyrosine kinase, which results in phosphorylation of insulin receptor substrates (IRSs) on multiple tyrosine residues. These phosphotyrosine residues act as docking sites for many SH2 domain–containing proteins, including the p85 regulatory subunit of phosphoinositide 3′ kinase (PI3K). Binding of the p110 catalytic subunit of PI3K to p85 activates the lipid kinase that promotes glucose transport. Whereas activation of PI3K is necessary for full stimulation of glucose transport by insulin, emerging evidence suggests that it is not sufficient and another pathway may also be necessary . The signals downstream of PI3K are still unknown, and there is controversy as to whether the serine/threonine kinase Akt/protein kinase B (PKB) or the protein kinase C (PKC) isoform λ/ζ mediates insulin stimulation of glucose transport. Most likely, the pathways that mediate insulin‟s metabolic effects diverge downstream of PI3K and show differential sensitivity to varying levels of insulin. For example, the antilipolytic effect of insulin requires much lower insulin concentrations than stimulation of glucose transport. Hence, even in insulin-resistant states in which glucose transport is impaired, sensitivity to insulin‟s antilipolytic effect is relatively preserved, resulting in maintenance or expansion of adipose stores. Insulin also activates the ras–mitogen-activated protein kinase (ras-MAPK) signaling cascade. This pathway appears to be important for the mitogenic effects of insulin, but most data do not implicate the MAPK pathway in the well-studied metabolic actions of insulin. Insulin action in adipocytes also involves changes in gene transcription. The transcription factor ADD-1/SREBP-1c (adipocyte determination and differentiation factor-1/sterol regulatory element–binding protein-1c) may play a critical role in the actions of insulin to regulate adipocyte gene expression,by inducing genes involved in lipogenesis and repressing those involved in fatty acid oxidation. Transcription factors of the forkhead family may also play a major role in transducing insulin signals to the nucleus. The relative functions of the ADD-1/SREBP-1c and forkhead pathways should be the subject of future research **(Kahn, Barbara B et *al*, 2000)**

II/3.2. Insulin resistance in obesity and type 2 diabetes :

The term “insulin resistance” usually connotes resistance to the effects of insulin on glucose uptake, metabolism, or storage. Insulin resistance in obesity and type 2 diabetes is manifested by decreased insulin-stimulated glucose transport and metabolism in adipocytes and skeletal muscle and by impaired suppression of hepatic glucose output . These functional defects may result, in part, from impaired insulin signaling in all three target tissues and, in adipocytes, also from downregulation of the major insulin-responsive glucose transporter, GLUT4. In both muscle and adipocytes, insulin binding to its receptor, receptor phosphorylation and tyrosine kinase activity, and phosphorylation of IRSs are reduced. There are also tissue-specific alterations: In adipocytes from obese humans with type 2 diabetes, IRS-1 expression is reduced, resulting in decreased IRS-1–associated PI3K activity, and IRS-2 becomes the main docking protein for PI3K. In contrast, in skeletal muscle of obese, type 2 diabetic subjects, IRS-1 and IRS-2 protein levels are normal but PI3K activity associated with both

IRSs is impaired.

One mechanism for the signaling defects in obesity may be the increased expression and activity of several protein tyrosine phosphatases (PTPs), which dephosphorylate and thus terminate signaling propagated through tyrosyl phosphorylation events. Some data indicate that at least three PTPs, including PTP1B, leukocyte antigen–related phosphatase (LAR), and src-homology-phosphatase 2, are increased in expression and/or activity in muscle and adipose tissue of obese humans and rodents. PTP1B and LAR have been shown to dephosphorylate the insulin receptor and IRS-1 in vitro. In fact, mice in which PTP1B has been knocked out have increased insulin sensitivity and resistance to diet-induced obesity, at least in part, due to increased energy expenditure. This suggests a regulatory role for PTP1B not only in insulin action, but also in energy homeostasis. Interestingly, the insulin sensitivity is present in muscle and liver but not in adipocytes. Whether there is a causal relationship between the insulin sensitivity and leanness/energy expenditure or whether these are regulated by independent signaling pathways is a key question.

Other mechanisms also contribute to insulin resistance in obesity. In morbid obesity, the expression of various insulin signaling molecules is reduced in skeletal muscle. In all forms of obesity and diabetes, a major factor contributing to the impaired insulin-stimulated glucose transport in adipocytes is the downregulation of GLUT4. However, in skeletal muscle of obese and diabetic humans, GLUT4 expression is normal and defective glucose transport appears to be due to impaired translocation, docking, or fusion of GLUT4-containing vesicles with the plasma membrane.

Although insulin resistance is characteristic of obesity and type 2 diabetes, it is not established that all of insulin‟s actions are impaired in individuals with both conditions. It is possible that hepatic lipogenesis and lipid storage are being driven to excess in adipose tissue, whereas other insulin effects related to glucose homeostasis are impaired. It will be important to identify the signaling pathways and transcription factors that could allow for such discordant actions of insulin **(Kahn, Barbara B et *al*, 2000)**

II/3.3. Reduced glucose disposed into adipose tissue in obesity :

The action of insulin to lower blood glucose levels results from suppression of hepatic glucose production and increased glucose uptake into muscle and fat. Muscle has long been considered the major site of insulin-stimulated glucose uptake in vivo, with adipose tissue contributing relatively little to total body glucose disposal. Support for this conclusion comes from the fact that measurements of 2-deoxyglucose uptake in vivo show at least ten times more glucose per milligram of tissue going into muscle than into white adipose tissue **(WAT)**. Because muscle mass is considerably greater than **WAT** mass, at least in lean rodents and humans, this observation has been taken to indicate the prominent contribution of muscle to glucose disposal. Although glucose transport into brown adipose tissue **(BAT)** is higher than in many muscle groups, the mass of BAT is small even in rodents, making this an unlikely site to account for large amounts of total body glucose uptake. Thus, it has been viewed as unlikely that diminished glucose uptake into fat could account for diminished whole body glucose uptake in obesity. However, transgenic studies have raised the possibility of a greater role for glucose uptake into fat in systemic glucose homeostasis than was previously believed. Overexpression of GLUT4 selectively in fat enhances whole body insulin sensitivity and

glucose tolerance even in overtly diabetic mice. Furthermore, knocking out GLUT4 selectively from fat results in a degree of insulin resistance similar to that seen with muscle-specific knockout of GLUT4 (unpublished observation). Whether this systemic insulin resistance results directly from the absence of adipose glucose transport or indirectly from possible effects of altered glucose uptake on the release of other molecules from adipocytes remains a key question. Likely candidates for indirect effects are FFA, leptin, or TNF-α, all of which are known to affect glucose homeostasis (see below). Undoubtedly there are other, as yet undiscovered, molecules from fat that influence systemic metabolism.

Further support for a potential direct role of adipocytes in regulating systemic glucose homeostasis comes from studies in which rodents or humans are treated with the β3 adrenergic agonist CL316,243. Since β3 adrenergic receptors are expressed almost exclusively in fat, effects of these agents would be expected to be initiated by alterations in fat. Treatment with CL316,243 results in enhanced sensitivity of both whole body glucose uptake and suppression of hepatic glucose production . These effects are accompanied by increased glucose uptake in adipose tissue with no effect in multiple muscle groups studied. Thus, increasing glucose uptake selectively in fat with β3 adrenergic receptor agonists may improve whole body glucose uptake, with the effects in fat indirectly resulting in increased insulin sensitivity in liver. Alternatively, β3 agonists may work by changing the release of some adipocyte product that influences systemic insulin sensitivity **(Kahn, Barbara B et *al*, 2000)**

II/3.4. The significance of the location of body fat for insulin resistance :

The relationship between obesity and insulin resistance is seen across all ethnic groups and is evident across the full range of body weights. Large epidemiologic studies reveal that the risk for diabetes, and presumably insulin resistance, rises as body fat content (measured by body mass index [BMI]) increases from the very lean to the very obese, implying that the "dose" of body fat has an effect on insulin sensitivity across a broad range . Although this relationship is seen with measures of adiposity such as BMI, which reflect general adiposity, it is critical to realize that all sites of adiposity are not equal in this regard. Central (intra-abdominal) depots of fat are much more strongly linked to insulin resistance, type 2 diabetes, and cardiovascular disease than are peripheral (gluteal/subcutaneous) fat depots. This fact about fat and insulin sensitivity has not been adequately explained. It is possible that an unknown common factor, either genetic or environmental, produces both insulin resistance and the central pattern of regional adiposity, and that central obesity does not actually cause insulin resistance. Alternatively, some biochemical feature of intra-abdominal adipocytes may directly influence systemic insulin sensitivity.

A leading hypothesis in this regard is that intra-abdominal adipocytes are more lipolytically active, in part due to their complement of adrenergic receptors. This would increase intraportal FFA levels and flux, which might inhibit insulin clearance and promote insulin resistance by mechanisms that are still uncertain. Hyperinsulinemia per se can cause insulin resistance by downregulating insulin receptors and desensitizing postreceptor pathways, as was confirmed by overexpression of insulin in livers of otherwise normal transgenic mice. This transgene resulted in an age-related reduction in insulin receptor expression, glucose intolerance, and hyperlipidemia without any primary genetic defect in insulin action or secretion. An alternative hypothesis is that, since adipocytes are now known to secrete many factors that are capable of exerting systemic effects , the array of factors secreted by intra-

abdominal adipocytes may be particularly harmful to systemic insulin sensitivity. So far, this hypothesis remains unproven **(Kahn, Barbara B et *al*, 2000)**

II/3.5. Adipocyte as endocrine cells :

Adipocytes are well known for their essential role as energy storage depots for triglycerides, from which energy is called forth at times of need in the form of FFAs and glycerol. However, data emerging over the past several years have established an additional role for the adipocyte that of secretory cell **(Figure 25)**. Adipocytes express and secrete numerous peptide hormones and cytokines, including TNF-α; plasminogen-activator inhibitor-1, which helps maintain hemostasis; angiotensinogen, whose proteolytic product regulates vascular tone; and leptin, which plays a central role in regulating energy balance. Adipose tissue can also produce active steroid hormones, including estrogen and cortisol. Through such secreted products, adipocytes possess the capacity to influence local adipocyte biology, as well as systemic metabolism at sites as diverse as brain, liver, muscle, β cells, gonads, lymphoid organs, and systemic vasculature. This realization raises many possibilities for additional links between adipose function and mass and insulin resistance, independent of the adipocyte‟s roles in energy storage and release **(Figure 24)**.

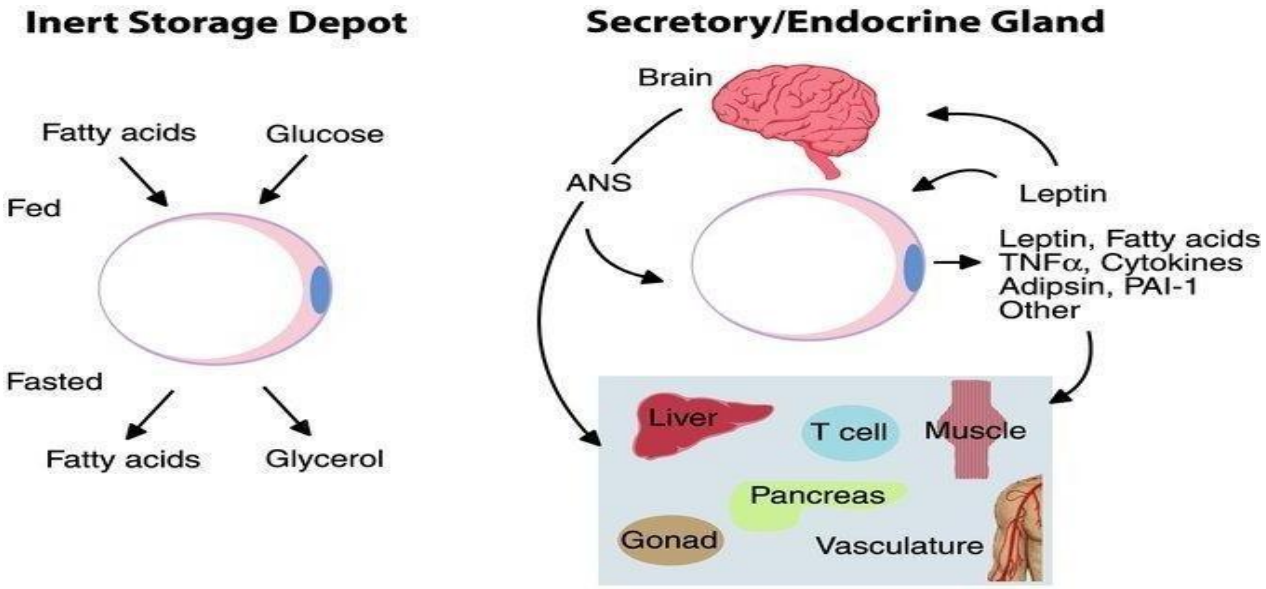


Figure 26 : Evolving view of the biological functions of the adipocyte. Previously, adipocytes were considered to be inert storage depots releasing fuel as fatty acids and glycerol in time of fasting or starvation. More recently it has become clear that adipocytes are endocrine glands that secrete important hormones, cytokines, vasoactive substances, and other peptides. ANS, autonomic nervous system **(Kahn, Barbara B et *al*, 2000)**

A great deal of interest has followed the discovery that adipocytes express and secrete the cytokine TNF-α, and that enlarged adipocytes from obese animals and humans overexpress this factor. Although not all studies have found TNF-α to be elevated in obesity, the normal circulating levels of this factor are at the limit of detection, making quantitative analysis uncertain. This low expression may indicate that TNF-α acts in a paracrine rather than endocrine fashion. Alternative approaches to assessing a role of TNF-α in systemic insulin resistance are therefore needed, and in some but not all studies using neutralizing antibodies

or other agents to block TNF-α function in animal models, it appears that such blockade heightens insulin sensitivity.

TNF-α has many effects on adipocyte function, and these include actions to inhibit lipogenesis and to increase lipolysis. These actions have been viewed by some as a feedback loop against excessive energy storage. Can excessive TNF-α cause insulin resistance? TNF-α signaling impairs insulin signaling, in part through serine phosphorylation of IRS-1, and can reduce GLUT4 gene expression, so a plausible cellular basis for TNF-α as a mediator of insulin resistance has been established. Further support derives from the beneficial effect of knockout of *TNFα* or *TNFα receptor* genes on insulin resistance in several animal models of obesity-associated insulin resistance. However, improvement of insulin resistance in response to loss of TNF signaling is at best partial, and the effect of TNF neutralization has not been seen in all experimental models. Thus, TNF-α may be a partial contributor to insulin resistance, but other factors must exist.

Leptin, the product of the *ob* gene, may be one such factor. This adipocyte-derived hormone exerts pleiotropic effects, including profound effects on satiety, energy expenditure, and neuroendocrine function. The most compelling role of leptin from an evolutionary standpoint is its capacity to serve as a bidirectional signal that switches metabolic physiology and neuroendocrine status between programs appropriate to the fed and starved states. The proposed role for rising leptin as a strong (adipostatic) signal to prevent obesity is easily subverted by leptin resistance. Since increased energy stores would favor survival in periods of famine, the adipostatic aspect of leptin action may have been selected against during the course of evolution. This view of leptin as being primarily involved in the starvation/feeding switch does not negate the fact that the absence of leptin in both rodents and humans produces severe obesity for which leptin is clearly the cure. Nor does it lessen the importance of determining the molecular basis for leptin resistance, which limits the capacity of rising leptin to prevent obesity in most situations.

Severe insulin resistance is a well-known feature of deficiency of leptin or its receptor in the *ob/ob* or *db/db* mouse strains, and these models were among the first to be investigated for the pathogenesis of insulin resistance in the early 1970s. Insulin resistance and hyperinsulinemia occur early in the life of these animals, are out of proportion to their adiposity at early stages, and exceed the insulin resistance and hyperinsulinemia due simply to hyperphagia and obesity. The degree to which diabetes (as opposed to insulin resistance without hyperglycemia) develops in these mice is determined by their genetic background, via effects on insulin secretory capacity and possibly other factors. The identity of these background modifier genes is unknown at present. Leptin‟s major site of action is the hypothalamus, especially in selected nuclei within the ventrobasal hypothalamus, where neurons that are directly regulated by leptin reside. The fact that hyperinsulinemia and insulin resistance are produced by hypothalamic lesions affecting the ventromedial hypothalamic nucleus suggested a major role for the central nervous system (CNS) in regulation of insulin action or secretion. Consistent with this model, current evidence suggests that leptin exerts much of its effect on metabolism and satiety through actions within the ventrobasal hypothalamus.

The result of leptin replacement in *ob/ob* mice on diabetes and insulin resistance is dramatic. Leptin treatment causes both glucose and insulin levels to fall within hours of administration, before changes in either food intake or body weight occur, and prolonged leptin has effects on

glucose and insulin that exceed those seen in pair-fed *ob/ob* mice. Leptin has a clear insulin-sensitizing effect acutely and also after chronic administration to normal rodents. The molecular basis for the insulin-sensitizing effect of leptin remains a topic of great interest. Two general views prevail. According to one, the metabolic actions of leptin are exerted predominantly through actions of leptin within the CNS, most likely within the hypothalamus (Figure 26). The hypothalamic pathways involved in these actions are incompletely understood, although a role for melanocortin signaling pathways has been suggested. These central effects may be transmitted to the periphery through a variety of mechanisms, including the effects of altered appetite to decrease nutrient flux into the body and the effects of leptin on neuroendocrine or neural pathways. Leptin‟s effects on insulin sensitivity likely extend beyond those caused by alterations in food intake and nutrient flux, so actions via neuroendocrine or neural effectors are most likely involved as well. In many rodent models of obesity, including those due to leptin deficiency or resistance, increased glucocorticoids are an important mediator of both hyperphagia and insulin resistance, as seen through the beneficial effects of adrenalectomy. In *ob/ob* mice, leptin replacement suppresses the activated hypothalamic-pituitary-adrenocortical (HPA) axis, which may be an important component of leptin‟s action on insulin sensitivity, at least in rodents. Autonomic nerves may also be involved, as suggested by the effects of denervation to reduce leptin‟s action to promote glucose uptake into some muscle types. Major unanswered questions at this point include which signaling mechanism(s) and cellular targets in the periphery respond to the autonomic nerve output by which leptin affects metabolic pathways in relevant tissues, such as muscle, liver, and fat.

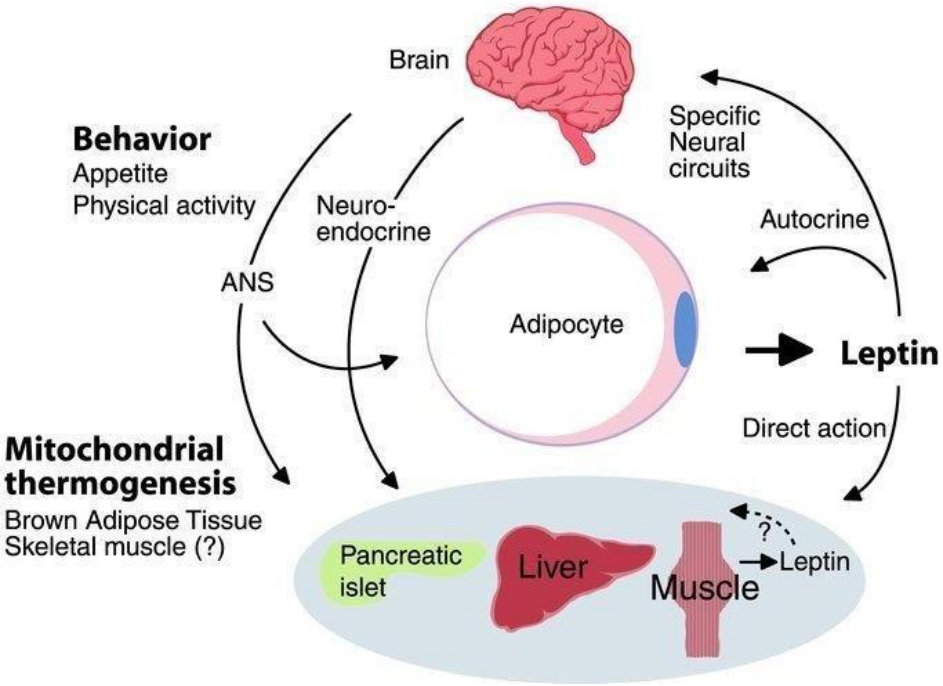


Figure 27 : Leptin exerts multiple actions to regulate glucose homeostasis through autocrine, paracrine, endocrine, and neural circuits. Whereas many of leptin‟s effects are mediated by the CNS, some effects may be exerted directly at the level of insulin target tissues or pancreatic islet cells **(Kahn, Barbara B et *al*, 2000)**

The second view of how leptin sensitizes to insulin involves direct effects at the level of insulin target tissues (Figure 26). In addition to the actions of leptin to modify metabolism via the brain, substantial data support the notion that leptin may have important effects through direct action on peripheral target cells, including β cells, liver, muscle, and fat. Although initial surveys suggested that the ObRb isoform of the leptin receptor was not expressed in peripheral tissues, it now appears that receptor expression in such tissues occurs at biologically meaningful levels, as assessed by the ability to rapidly activate signaling events, including activation of STAT and MAPK pathways. Some evidence suggests that in tissues including muscle and β cells, leptin promotes lipid oxidation and inhibits lipid synthesis, which would promote insulin sensitivity. Current data do not allow determination of the relative importance of central versus peripheral actions of leptin in the metabolic actions of the hormone with certainty. Since leptin fails to reverse insulin resistance and lipid accumulation in mice with ventromedial hypothalamic lesions, and low-dose central administration of leptin has major metabolic effects without changing blood leptin levels, it seems likely that central actions are required, and that without them, the peripheral actions are at best limited. Since leptin expression is induced in tissues such as skeletal muscle after periods of feeding, it is possible that leptin produced locally has important metabolic actions as well. Tissue-specific knockout of leptin receptor isoforms may be helpful in clarifying this point. Even if, as we suspect, leptin‟s major actions are exerted within the CNS, we lack insight into the precise mechanism by which engaging central neural pathways rapidly changes the ability of leptin to regulate metabolic pathways in the periphery. This area will surely attract attention from the research community.

Unlike rodents, the few humans with leptin or leptin receptor mutations and obesity do not appear to have extraordinary degrees of insulin resistance, as assessed by hyperinsulinemia, and none have as yet been described with diabetes. This difference may be related to the fact that in humans, unlike mice, leptin has little effect on the HPA axis. If leptin proves to have an important action on insulin sensitivity in humans, as it does in mice, then it will be important to determine the extent to which decreased leptin action, or leptin resistance, contributes to the insulin resistance of obesity in humans **(Kahn, Barbara B et *al*, 2000)**

II/3.6. Lipotoxicity and lipoatrophy : two sides of the same coin ? :

There are two additional ways in which alterations in the function of adipose tissue may influence glucose homeostasis. In one, increased adipose energy storage in obesity results in increased FFA flux to other tissues and increased triglyceride storage in these tissues, which promote insulin resistance and other adverse effects, referred to by some as “lipotoxicity.” In the other, paradoxically, the absence of adipose tissue begets many of the same outcomes. How do we explain this paradox?

When the adipose depot is expanded, as in obesity, plasma FFAs become elevated, due, most likely, to increased release from the expanded adipose mass and probably also to impaired hepatic metabolism. Elevated FFAs impair the ability of insulin to suppress hepatic glucose output and to stimulate glucose uptake into skeletal muscle, as well as to inhibit insulin secretion from pancreatic β cells. The defect in muscle may involve impaired activation of PI3K, possibly due to elevations in PKCθ . An acquired loss of PI3K activation in muscle is

also seen as a result of a high-fat diet. In humans, the triglyceride content of muscle correlates directly with insulin resistance, and the fatty acid composition of muscle phospholipids influences insulzzin sensitivity. We need to learn much more about the mechanisms that drive lipid accumulation in nonadipose tissues, and the mechanisms by which such lipotoxic impairment of function occurs. Recent studies in β cells suggest that long-chain fatty acids may exert adverse effects via inducing overproduction of ceramide. It will be important to determine whether fatty acids alter gene expression through binding as ligands to transcription factors of the peroxisome proliferator–activated receptor (PPAR) family.

Severe deficiency or absence of fat occurs in patients with a heterogeneous group of disorders known as lipodystrophic diabetes, which, remarkably, is also associated with severe insulin resistance. It has been suggested that certain inherited disorders of insulin signaling pathways might account for both aspects of the disorder. However, thus far, no inherited defects in the insulin signaling pathway have been identified in these patients, and patients with insulin receptor mutations and insulin resistance do not have lipoatrophy. An alternative hypothesis, now supported by some published findings, holds that a primary deficiency of adipose tissue would cause severe insulin resistance. Two different mouse models in which fat is reduced or missing completely due to a disruption of adipogenesis has now been shown to have severe insulin resistance. In one case, leptin alone reversed the insulin resistance and diabetes. In the other, which shows more complete adipose loss, leptin replacement transiently ameliorated but did not reverse the disorder, whereas fat transplantation dramatically reversed insulin resistance and diabetes. Thus, it is clear that leptin and, possibly, other uncharacterized adipocyte products influence insulin sensitivity in the mouse.

That lipoatrophy causes insulin resistance by deficiency of secretory products of adipocytes, as opposed to the storage function alone, is also seen from studies of a “skinny” mouse, made deficient in adipose tissue through transgenic overexpression of leptin. Unlike lipoatrophic mice that lack leptin, these hyperleptinemic mice lacking visible adipose tissue have increased insulin sensitivity and do not accumulate triglyceride in muscles or liver. This may be due to the increased metabolic rate and body temperature in these mice, which result in increased substrate utilization instead of fat storage, as well as to effects of leptin to increase fatty acid oxidation (whether through the CNS or directly in peripheral tissues). Leptin increases fatty acid oxidation and decreases esterification in skeletal muscle and in pancreatic islets. This appears to be due, at least in part, to regulation of the expression of genes involved in fatty acid metabolism and may be exerted directly at the level of the target tissues, as the effects are seen in muscle and islets exposed to leptin ex vivo. In islets of obese Zucker diabetic fatty rats with leptin receptor mutations, triglyceride content is 20 times greater than in lean controls and esterification capacity is increased three- to fourfold. Maneuvers that reduce islet fat content improve insulin secretion and prevent diabetes in these rats **(Kahn, Barbara B et *al*, 2000)**

II/4. Glucotoxicity :

Glucose toxicity is a well-established entity that has been shown in animal models of diabetes to contribute to development of insulin resistance and impaired insulin secretion. In type II (non-insulin-dependent) diabetes in humans, a considerable body of evidence has accumulated indicating that a chronic physiological increment in the plasma glucose concentration leads to progressive impairment in insulin secretion and may contribute to insulin resistance as well. The precise biochemical mechanism(s) responsible for the

hyperglycemia-induced defect in insulin secretion remains to be defined but may be related to a defect in phosphoinositide metabolism. In animal models of diabetes, development of insulin resistance is related to downregulation of the glucose-transport system, and a similar phenomenon is also likely to occur in humans. In addition, hyperglycemia in humans may lead to a defect in glycogen synthesis. In this respect, humans may be different from rats. In type I (insulin-dependent) diabetic patients who are poorly controlled, insulin resistance is a characteristic feature and can be ameliorated by tight glycemic control, suggesting that hyperglycemia is responsible for the insulin resistance. Evidence also has accumulated to implicate glucose toxicity in the functional impairment in insulin secretion that occurs during the initial presentation of patients with type I diabetes, and this may explain the honeymoon period so commonly observed after the institution of insulin therapy **(Rossetti, Lciano et *al,* 1990)**

II/4.1. Lipotoxicity :

Enlarged fat cells in obese adipose tissue diminish capacity to store fat and are resistant to the anti-lipolytic effect of insulin. Insulin resistance (IR)-associated S-nitrosylation of insulin-signaling proteins increases in obesity. In accordance with the inhibition of insulin-mediated anti-lipolytic action, plasma free fatty acid (FFA) levels increase. Additionally, endoplasmic reticulum stress stimuli induce lipolysis by activating cyclic adenosine monophosphate/Protein kinase A (cAMP/PKA) and extracellular signal-regulated kinase ½ (ERK1/2) signaling in adipocytes. Failure of packaging of excess lipid into lipid droplets causes chronic elevation of circulating fatty acids, which can reach to toxic levels within non-adipose tissues. Deleterious effects of lipid accumulation in non-adipose tissues are known as lipotoxicity. In fact, triglycerides may also serve a storage function for long-chain non-esterified fatty acids and their products such as ceramides and diacylglycerols (DAGs). Thus, excess DAG, ceramide and saturated fatty acids in obesity can induce chronic inflammation and have harmful effect on multiple organs and systems. In this context, chronic adipose tissue inflammation, mitochondrial dysfunction and IR have been discussed within the scope of lipotoxicity **(Engin, Ayse Basak, 2017)**

II/4.2. Adipokines :

Adipokines act centrally to regulate appetite and energy expenditure, and peripherally affect insulin sensitivity, oxidative capacity, and lipid uptake. Nevertheless, as a dynamic organ, the adipokine profile changes in response to the amount and condition of adipose tissue. Thus, in obesity, the release of adipokines leads to metabolic disturbances that could play a central role in the development of insulin resistance, type 2 diabetes and the increased risk of cardiovascular disease. The aim of this review is to describe the obesity specific-adipokine profile and the role of some adipokines in obesity-related metabolic disorders **(de Oliveira Leal et *al*, 2013)**

Adipokines, released by either adipocytes or adipose tissue-infiltrated macrophages in response to fat mass expansion characteristic of obesity, induce low-grade chronic inflammation, insulin resistance and atherogenic effect. Although the role of some adipokines in obesity remains unclear, reduced concentration of adipokines such as adiponectin, omentin and ZAG are associated with beneficial effects. Concomitantly, obesity is accompanied by increased proinflammatory cytokines and atherogenic **(de Oliveira Leal et *al*, 2013)**

II/6. Oxidative stress :

Extramitochondrial oxygen consumption can occur by nonenzymatic and other enzymatic reactions, including NADPH oxidase, xanthine oxidase, uncoupled NO synthase, D-aminooxidase, p450 cytochromes, and proline hydroxylases; however, mitochondria are the major sites of ROS production (0.2% to 2% of total oxygen taken by cells). ROS production occurs mainly at complex I (NADH CoQ reductase) and complex III (bc_1 complex) in mitochondria. ROS production is increased when excess electrons are provided to mitochondrial respiratory chains. The excess electrons are transferred to oxygen, which is converted to superoxide and subsequently to hydrogen peroxide either by spontaneously or via superoxide dismutase. The highest rate of ROS production occurs when the proton gradient is high and oxygen consumption (ATP demand) is low. Excess calorie intake and low energy expenditure can cause high proton-motive force and less ATP demand. Therefore, most electron carriers are occupied by electrons, and excess electrons are transferred to oxygen without ATP production. When exercise increases ATP demand, electron transfers are coupled to ATP production and reduce proton-motive force. Despite intracellular protective mechanisms, including superoxide dismutase, catalase, and reduced glutathione, excess ROS is detrimental to cellular physiology. ROS generated from mitochondria damages proteins, DNA, and lipid in membrane components, which results in mitochondrial dysfunction **(Kim, Jeong-A et *al*, 2008)**

II/7. Mitochondrial dysfunction :

Aerobic organisms consume oxygen to produce energy from nutrients. In eukaryotic cells, energy production, mostly in the form of ATP, is controlled by mitochondria that link oxidative respiration with metabolism of nutrients (Figure 27). Mitochondria are compartmentalized by outer and inner membranes, and the mitochondrial respiratory chain is located in the inner membrane. Production of ATP requires 2 major steps, oxidation of NADH (or $FADH_2$) and phosphorylation of ADP to form ATP (oxidative phosphorylation [OXPHOS]). These 2 reactions are coupled in mitochondria, and OXPHOS is an efficient and energy-conserving way of producing energy in aerobic organisms. NADH or $FADH_2$ are generated during glucose metabolism via glycolysis and the tricarboxylic acid cycle or β-oxidation of fatty acids. NADH or $FADH_2$ are oxidized to NAD^+ or FAD while protons are pumped to the intermitochondrial membrane through respiratory complexes I, III, and IV. Electrons from NADH or $FADH_2$ are then transferred through a series of respiratory chain complexes to O_2, which finally generates H_2O. A proton gradient across the membrane is the driving force of F_0F_1-ATPase (ATP synthase) to produce ATP from ADP. ATP is transported to the cytosol by exchanging with ADP through adenine nucleotide translocator and used for various biological events that require energy. On the other hand, mitochondria generate heat by a mechanism called “proton leak.” Proton leak from the intermembrane space to matrix (uncoupling) reduces proton-motive force and generates heat instead ATP. Uncoupling proteins (UCPs) play a major role in reducing the proton gradient. UCP1 is expressed almost exclusively in brown adipose tissue. UCP2 is ubiquitously expressed, and UCP3 is expressed in skeletal muscle. UCP1, up to 10% of membrane protein, regulates adaptive thermogenesis, whereas UCP2 and -3 do not appear to play a major role in thermogenesis; mice with genetic ablation of UCP2 and -3 display a normal response to cold, normal basal proton conductance, and normal body weight. Indeed, overexpression of UCP2 or -3 lowers reactive oxygen species (ROS) production, stimulates the metabolic rate, and protects against weight gain and

insulin resistance. Moreover, UCP3 knockout mice show severe oxidative damage. Collectively, these results suggest that UCPs play an important role in mitochondrial function by regulating both heat and ROS generation. Mitochondrial function with regard to energy balance is important in normal physiology and cellular function **(Kim, Jeong-A et *al*, 2008)**

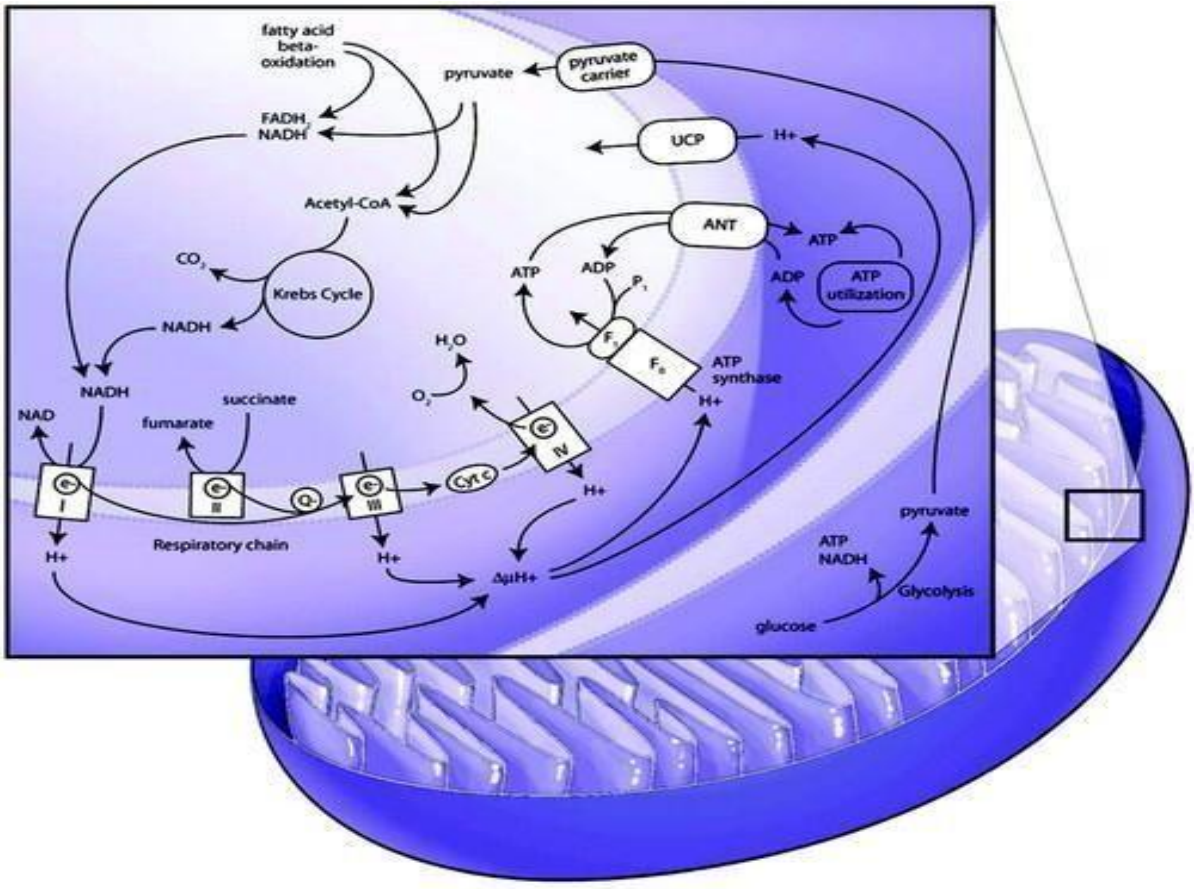


Figure 28 : Mitochondrial respiratory chain and nutrient metabolism. Reducing agents (NADH or $FADH_2$) are generated from glycolysis and Krebs cycle of glucose metabolism and β-oxidation of fatty acids. While NADH or $FADH_2$ are oxidized to NAD^+ or FAD, the electrons are carried to complex I (NADH–ubiquinone reductase), complex II (succinated ubiquinone reductase), complex III (ubiquinone–cytochrome *c* reductase), complex IV (cytochrome oxidase), and finally to O_2, which produces H_2O. Oxidation of NADH or FADH2 generates protons that are pumped to intermembrane space through complex I, III, and IV. The pumped protons increase electrochemical gradient across the membrane. This proton gradient is the driving force for F0F1-ATPase (ATP synthase) to produce ATP, which is used as an energy source in the body. On the other hand, the pumped protons can be leaked to matrix of mitochondria by UCP, which reduces proton gradient and in turn generates heat. Producing ATP or heat is controlled by energy needs in the body. ANT indicates adenine nucleotide translocator **(Kim, Jeong-A et *al*, 2008)**

There is evidence that mitochondrial dysfunction is associated with T2DM and age-related insulin resistance (Figure 28). Genetic factors, oxidative stress, mitochondrial biogenesis, and aging may affect mitochondrial function, leading to insulin resistance and various

pathological conditions.

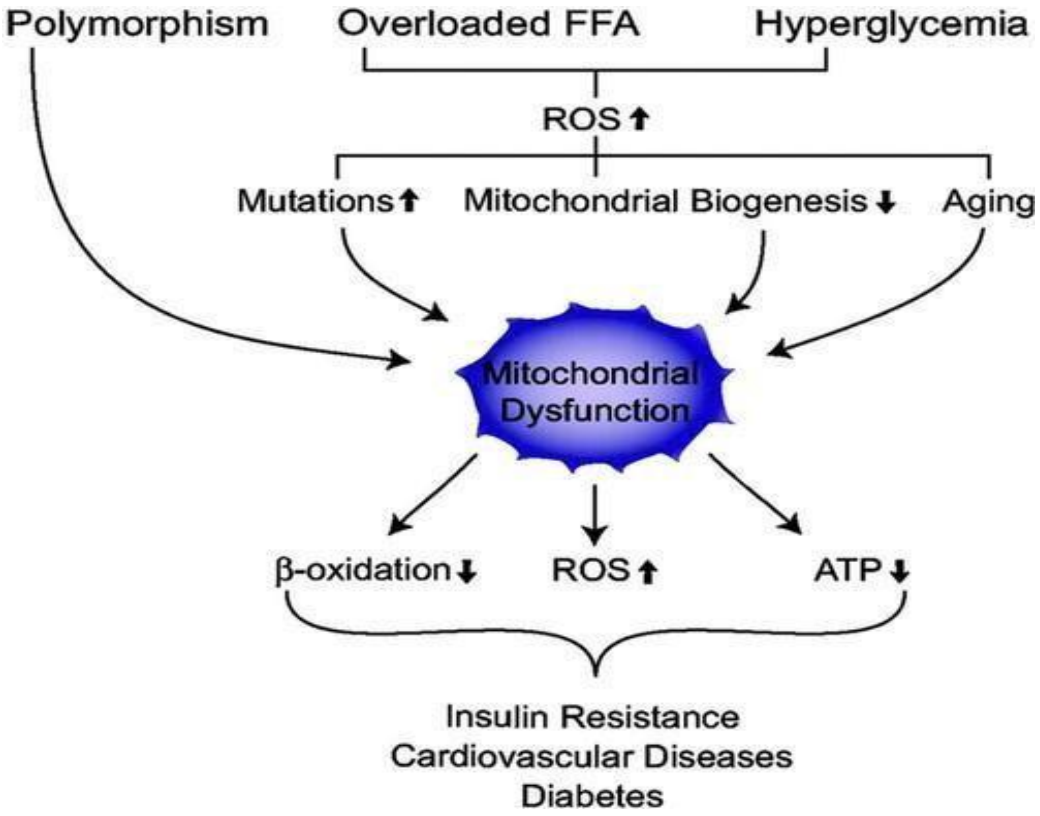


Figure 29 : Mechanism of mitochondrial dysfunction. Excess intake of nutrients, including overloaded FFAs or hyperglycemia conditions, increases ROS production and reduces mitochondrial biogenesis, causing mitochondrial dysfunction. Mitochondrial dysfunction leads to decreased β-oxidation and ATP production and increased ROS production, resulting in insulin resistance, diabetes, and cardiovascular disease **(Kim, Jeong-A et *al*, 2008)**

II/7.1. Endoplasmic reticulum (ER) stress :

The endoplasmic reticulum (ER) is a central organelle entrusted with lipid synthesis, protein folding and protein maturation. It is endowed with a quality control system that facilitates the recognition and targeting of aberrant proteins for degradation. When the capacity of this quality control system is exceeded, a stress response (ER stress) is switched on. Prolonged stress leads to apoptosis and may thus be an important factor in the pathogenesis of many diseases. A complex homeostatic signaling pathway, known as the unfolded protein response (UPR), has evolved to maintain a balance between the load of newly synthesized proteins and the capacity of the ER to aid in their maturation. Dysfunction of the UPR plays an important role in certain diseases, especially those involving tissues dedicated to extracellular protein synthesis. Diabetes is an example of such a disease, since pancreatic β-cells depend on efficient UPR signaling to meet the demands for constantly varying levels of insulin synthesis. Recent studies have indicated that the importance of the UPR in diabetes is not restricted to the β-cell but also to tissues of peripheral insulin resistance such as liver and adipose tissue. Better understanding of the basic mechanisms of ER stress and development of insulin resistance/type 2 diabetes is pivotal for the identification of newer molecular targets for therapeutic interventions **(Rajan, S, Sundar, et *al*, 2007)**

The endoplasmic reticulum (ER) stress response, also commonly known as the unfolded protein response (UPR), is an adaptive response used to align ER functional capacity with demand. It is activated in various tissues under conditions related to obesity and type 2 diabetes. Hypothalamic ER stress contributes to inflammation and leptin/insulin resistance. Hepatic ER stress contributes to the development of steatosis and insulin resistance, and components of the UPR regulate liver lipid metabolism. ER stress in enlarged fat tissues induces inflammation and modifies adipokine secretion, and saturated fats cause ER stress in muscle. Finally, prolonged ER stress impairs insulin synthesis and causes pancreatic β cell apoptosis. In this review, we discuss ways in which ER stress operates as a common molecular pathway in the pathogenesis of obesity and diabetes **(Cnop, Miriam et *al*, 2012)**

II/7.2. Mitochondrial dysfunction and insulin resistance :

Mitochondrial dysfunction was first described in the context of glucose intolerance ~40 years ago , and the majority of studies in this area since that time have focussed on changes in skeletal muscle, which will be the main organ discussed in this review. Several studies in humans (from the late 1990s) suggested the existence of mitochondrial dysfunction in obese and insulin-resistant patients, with these individuals exhibiting lower oxidative enzyme activities and decreased lipid metabolism in muscle compared with lean control subjects. In addition, Kelley et al. published in 2002 that skeletal muscle of obese subjects with type 2 diabetes (T2D) exhibited lower NADH:O2 oxidoreductase activity and reduced mitochondrial size when compared with lean control subjects. One year later, two major microarray studies carried out in muscle showed mitochondrial biogenesis and oxidative phosphorylation pathways to be downregulated in T2D patients and non-diabetic individuals with a family history (FH+) of T2D when compared with healthy controls. These two studies were of particular interest to metabolic researchers as i) they showed a decrease in peroxisome proliferator coactivator 1a (PGC1α), the master regulator of mitochondrial metabolism , and therefore for the first time suggested a mechanism for the decrease in mitochondrial function, and ii) they provided evidence for genetic predisposition to mitochondrial defects and its occurrence in the „pre-diabetic" state. Following these initial observations, several studies in humans showed similar downregulation of metabolic and mitochondrial pathways in obesity and IR. Defects in the expression of mitochondrial genes were found at the mRNA level as well as at the protein level; this was accompanied by a decrease in oxidative enzyme activity and mitochondrial size and density. To some extent, it still remains unclear whether the observed defects could be primarily due to a decrease in the number of mitochondria „per unit of muscle tissue" or due to actual metabolic changes within the mitochondria. Disparate results have also been reported with regards to the intramuscular populations of mitochondria that are affected (subsarcolemmal vs intermyofibrillar) and between different muscles across the body.

Although several human (as above) as well as rodent studies have described associations between diminished mitochondrial function and obesity/IR, various independent publications have failed to show such a correlation. For example, several studies have shown that muscle mitochondrial function was not impaired in obese and T2D human subjects when compared with controls. In addition, non-obese sedentary humans that were overfed for 28 days exhibited peripheral IR (determined as a decrease in glucose infusion rate during hyperinsulinemic–euglycaemic clamps) without changes in several markers of mitochondrial

content in muscle. Similarly, rats fed a high-fat diet exhibited unchanged mRNA levels of various energy and glucose metabolism markers in muscle, as well as similar hepatic mitochondrial and peroxisomal fatty acid oxidation capacity when compared with low-fat diet controls.

Besides evidence for scenario 1 (a decrease in mitochondrial function with IR) and scenario 2 (unchanged mitochondrial function despite IR), several research groups, including ours, have shown a compensatory increase in mitochondrial oxidative capacity with increased lipid supply. Mice and rats fed high-fat diets exhibited impairments in glucose tolerance and insulin sensitivity, but simultaneously an increase in fatty acid oxidative capacity, as well as protein content and activity of mitochondrial oxidative proteins in muscle . Both the increase in mitochondrial content and oxidative capacity, as well as the development of IR , occur at around 3–4 weeks of high-fat feeding. Furthermore, in a recent comparison of mouse strain, our group showed that this mitochondrial adaptation to high-fat feeding was present in several different mouse strains (C57BL/6, 129X1, DBA/2 and FVB/N) that were prone to fat-induced obesity and glucose intolerance. The implications from these studies are that while there is a compensatory increase in mitochondrial oxidative capacity in rodents in response to dietary lipid oversupply, the timing and magnitude of these changes are not sufficient to cope with the dramatically enhanced lipid availability, and thus there is still ectopic lipid accumulation and IR. In support of this, dietary or genetic manipulations that enhance oxidative capacity in muscle above the normal adaptive response do ameliorate IR.

Collectively, the three possible scenarios described above (i.e. decreased, unchanged or a compensatory increase in mitochondrial function) suggest that mitochondrial dysfunction is not a requisite feature of IR in all circumstances and the presence of mitochondrial dysfunction is dependent on its definition, the population studied, the model system examined (e.g. human vs rodent models) and the methodological approach (e.g. association vs intervention studies) **(Montgomery, Magdalene K, et *al*, 2015)**

II/8.Vitamin D status in obese diabetics :

II/8.1.Relationship between Vitamin D and obesity:

The association between reduced 25D concentrations and obesity is well established, and can be adequately accounted for by a volumetric, dilutional model. Correction of low 25D concentrations in obese individuals requires higher doses than those often advocated for the general population.

There are plausible mechanisms and some in vitro evidence supporting a role for vitamin D in weight reduction, with the proviso that it may be difficult to determine which effects are due to vitamin D itself and which are mediated via calcium. Clinical trials have not been conclusive, at least in part due to variable quality of study design. Some studies showing no effect of vitamin D supplementation on weight included participants who were vitamin D replete, and may thus have shown that giving supplemental vitamin D to those who are replete has no additional effect. There is a clear need for adequately-powered, prospective interventions which include baseline measurement of 25D concentrations and involve adequate doses of supplemental vitamin D. Until such studies have been reported, the role of vitamin D supplementation in obesity prevention remains uncertain **(Vanlint, Simon, 2013)**

Currently, vitamin D deficiency and obesity are pandemic diseases and they are associated with cardiovascular (CV) disease, metabolic syndrome and type 2 diabetes mellitus (T2DM) and other diseases. Concentrations of 25-hydroxyvitamin D (25(OH)D) (25D) are considered as the best indicator of total body vitamin D stores. An association between reduced circulating 25D concentrations and obesity is well known, but the mechanisms are not totally clear. The role of vitamin D supplementation is still uncertain and prospective interventions will establish its influence, if any, in the treatment of obesity. Vitamin D deficiency is associated with the presence of a cardiometabolic risk profile in the obese. Future trials may establish a role for Vitamin D supplementation in individuals at increased CV risk **(Soskić, Sanja et *al*, 2013)**

There are four suggested mechanisms that are most commonly cited within the literature which may explain a low vitamin D status in obesity: (1) obese individuals have decreased sun exposure compared with their lean counterparts; (2) negative feedback from an increased 1,25(OH)D concentration in obese individuals decreases 25(OH)D concentrations; (3) vitamin D is sequestered within adipose tissue; (4) lower 25(OH)D concentration is simply due to volumetric dilution **(Pourshahidi, L, Kirsty, 2015)**

II/8.2. Relationship between vitamin D and type 2 diabetes :

Vitamin D deficiency is mainly a consequence of insufficient sunlight induced vitamin D production in the skin and has been associated with various chronic diseases including type 2 diabetes. Experimental data have shown that vitamin D is important for glucose induced insulin secretion, improves insulin resistance, and exerts anti-inflammatory actions. Epidemiological studies have largely documented that a poor vitamin D status is associated with higher risk of insulin resistance and type 2 diabetes. The majority of randomized controlled trials (RCTs) in healthy or prediabetic individuals have, however, failed to demonstrate relevant vitamin D effects on insulin resistance or diabetes incidence. In patients with type 2 diabetes, a few RCTs reported some moderate effects of vitamin D on glycemic control and insulin resistance. While these findings warrant further in-depth studies, the current evidence is insufficient to recommend vitamin D supplementation for the prevention or treatment of type 2 diabetes **(Pilz, Stefan, et *al*, 2013)**

Type 2 diabetes mellitus (T2DM) has become a significant global health care problem and its reported incidence is increasing at an alarming rate. Despite the improvement in therapy and development of new drugs, treatment still remains insufficient especially due to the associated side effects of most available drugs. Efforts are continuing toward disease prevention and search for safer drugs. Conflicting evidence is associating low levels of vitamin D in the body to T2DM and as such studies have been conducted to test the effect of vitamin D levels on incidence of diabetes, diabetic control as well as diabetic complications.

Despite the conflicting evidence, vitamin D replacement seems to have some beneficial effect on the many aspects of diabetes: incidence, control and complications. Further long term and more convincing controlled trials are required in order to draw firmer conclusions on this beneficial role of vitamin D treatment on T2DM **(Issa, Claire Michael, 2017)**

II/8.3. Relationship between vitamin D and BMI :

The deficiency of vitamin D is associated with an increased level of BMI in the studies of both diabetic and non-diabetic subjects. Reliable evidence from well-designed future

randomized controlled trials is required to confirm the findings from observational studies and to find out the potential regulatory effects of vitamin D supplementation to lower BMI.

The current meta-analysis demonstrated an inverse relationship between vitamin D status and BMI in both the diabetic and non-diabetic subjects, however, this association was more pronounced in the diabetic patients. The correlation was directly related to the BMI quartiles and the highest BMI quartile had the strongest correlations in both the diabetic and non-diabetic populations. In the subgroup analysis of the diabetic subject studies, an abrupt increase in the correlation in the higher quartile showed the positive relationship of hypovitaminosis D, obesity, and type 2 diabetes **(Rafiq, Shamaila et *al*, 2018)**

II/8.4. Relationship between vitamin D and IR :

Vitamin D is not only a regulator of bone and mineral metabolism, but also a potent immunomodulator linked to many major human diseases including glucose homeostasis and insulin resistance. Vitamin D deficiency has been shown to affect insulin secretion in both humans and animal models. Accumulating evidence suggests the role of vitamin D in the pathogenesis of insulin resistance including several vitamin-D-related gene polymorphisms and vitamin-D-related metabolic and immune pathways. Supplementations of vitamin D may provide for suitable management and act to ameliorate insulin resistance. Additionally, there is a need for randomized trials to evaluate the significant effects of vitamin D supplementations in insulin resistance **(Sung, Chih-Chien, et *al*, 2012)**

It seems that vitamin D can improve diabetes control and it is recommended that vitamin D supplementation should be included in treatment of type 2 diabetes **(Talaei, Afsaneh et *al*, 2013)**

CHAPTER III : MATERIALS AND METHODS

III /1.Materials :

We chose the hospital establishment, brothers CHENAFA, Mecheria, Wilaya of Naama. After getting approval from the hospital director to allow us to enter the internal medicine department. We undertook to collect the information necessary for our graduation thesis.

III /1.1. The objective of the study :

The main objective of our study is to determine the incidence and assess the frequency of type II diabetes caused by obesity. As well as the determination of the most frequent risk factors associated with type II diabetes and evaluate the complications associated with this pathology and the frequency of use of alternative treatments in diabetics.

III /2. Methods :

III /2.1. Study Strategy :

Our study is mixed, retrospective and prospective, based on two parts, the first is quantitative, using a preestablished questionnaire, intended for diabetic patients included in study. The second component is qualitative, the main tool of which is the observation and analysis of medical data of patients with type 2 diabetes and also interviews with doctors generalists working at the hospital level.

III /2.1.1. Target population and sampling :

III /2.1.1.1. Target population :

Study population All hospitalized type 2 diabetic patients were randomly followed up.

III /2.1.1.1. A. Inclusion criteria :

The inclusion criteria were patients with diabetes mellitus From 2002 to 2019 years, diagnosed with fasting blood glucose greater than or equal to 1.26 mg/l and glycated haemoglobin (HbA1C) greater than or equal to 6.5% and there BMI normal should be between 18.5 to 24.9 .

III /2.1.1.1. B. Non-inclusion criteria :

The main exclusion criteria were smoking, pregnant or lactating women, people receiving vitamin complexes and antioxidant supplements, patients with hypertension, renal or heart or liver disease, dyslipidemia and acute infection.

III /2.1.1.2. Sampling method and sample size :

We conducted a descriptive epidemiological study that took place three months, from the 28/12/2022 to 28/05/2023.

After the administrative procedures for obtaining the authorization of access to the establishments, we introduced ourselves and explained our work to the hospital staff.

For this purpose, we collected data from a pre-arranged questionnaire of patients by chance (patients who have an appointment) and we also collected clinical and paraclinical data

recorded in the patients' medical records.

III /2.1.1.3.Sample :

Our sample consists of 510 people with type II diabetes.

III /2.2. Data collected and data collection tools :

III /2.2.1. Questionning : (annexe I)

For the purpose of gathering data, we created a questionnaire (Appendix 01) with 12 questions. It is targeted at diabetics and uses straightforward language to avoid any potential ambiguity for patients. There are various parts to it.

- **Gender :** Female / Male
- **Age:** Age ranges were established in a range of 20 to 100
- **Lifestyle habits:** these include:

  - Cigarette smoke (tobacco).

  - Feeding.

  - Physical activity.

- **Family history of diabetes:** We also looked for the character of familial diabetes.
- **Weight:** is measured with a scale, with an extent of 150 Kg, the patient is motionless in the center of the tray, the weight is distributed equally over the two pieds.la reading of the weight is done directly on the display screen.
- **Size:** is measured with a flask that measures the patient's height.
- **Waist circumference:** is measured with a tape measure pass at the distance between the last palpable dimension and the iliac crest.
- **Body mass index BMI:** estimates the degree of obesity.
- **Blood glucose:** the measurement of blood glucose makes it possible to assess the level of sugar in the blood (taking the first and last blood glucose reading).
- **HbA1c:** Below 7% is a good result, between 7% and 8% is average, between 8% and 10% is not good and beyond 10 is catastrophic.
- **The lipid balance:** this assessment of fat levels (lipids) in the body Measurement of triglycerides and cholesterol makes it possible to assess the risk of cardiovascular complications in diabetics.

III /2.2.2. Consulting documents :

To collect the data, we reviewed various records of patients with type 2 diabetes and consultation records in hospital records.

III /2.3. Difficulties encountered :

In carrying out this work, we have encountered difficulties. I quote specifically here:

- Some files have been demoted due to typos or missing information can help us.
- Difficulty explaining the purpose of our work to the subjects.
- The unavailability of some subjects and the non-cooperation of others, in particular

Year.

- If an employee of the admissions office is absent due to his obligations.
- Difficulty deciphering information in patient records.
- Poor filing of patient records in archives.

III /2.4. Interviews :

Interviews were conducted according to pre-established guidelines with two general practitioners from the hospital treating the patient in question.

The needs of patients (diabetics) were identified using qualitative methods. Indeed, our approach is community-driven with patient-centered applications. We used a ready-made guide to refine the questions we discuss.

III /2.5. Ethical considerations :

The participation of diabetics participating in our study is entirely voluntary and the patient's first and last name is not displayed on the form.

III /2.6. Statistical processing of data :

Statistical tests were performed using Microsoft office excel 2019 for the analysis of quantitative data collected through the questionnaire.

CHAPTER IV : RESULTS AND DISCUSSION

IV /1. Modifiable risk factors :

This is a descriptive retrospective study of 510 patients with type 2 diabetes with a sex ratio M/W=156/354: 0.44 whose results allowed us to identify the following distribution:

IV /1.1. Gender :

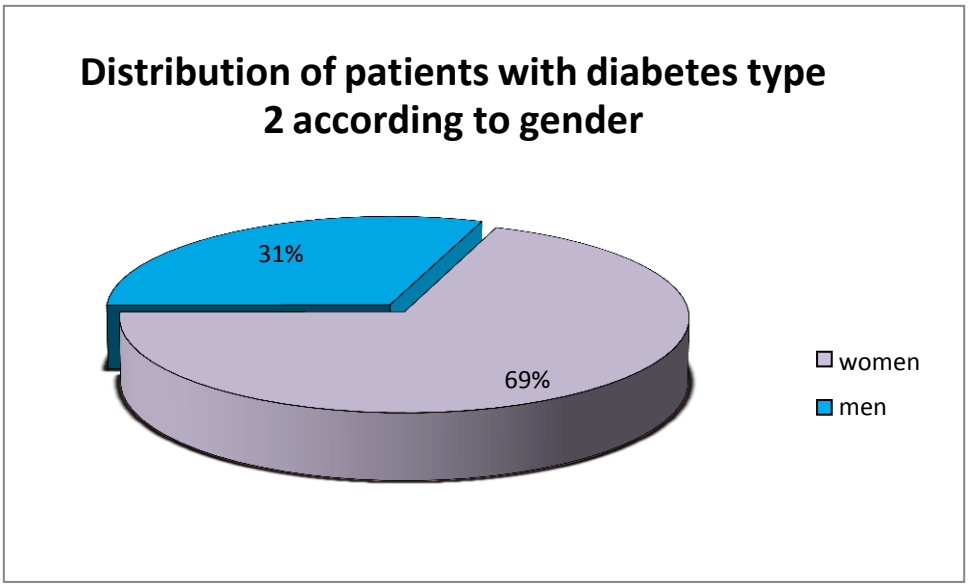


Figure 30 : Distribution of patients with diabetes type 2 according to gender.

In our study, women make up 69.41% of the population. Higher prevalence in female subjects compared to male subjects representing 30.59%.

This dominance is explained by the lack of respect for male reluctance. A man comes to the hospital only to write a prescription. Our study also ran from morning until noon. Most men are employed, unlike women who consult regularly.

Type II diabetes showed a pronounced female excess in the first half of the last century but is now equally prevalent among men and women in most populations, with some evidence of male preponderance in early middle age.

However, studies have shown that Women are more affected by diabetes with a percentage of 53.06% compared to men who represent the 46.93%. **(Zghebi, Salwa S, et *al*, 2017)**

IV /1.2. Age :

The age at which people develop type 2 diabetes varies from person to person. After reviewing patient records, we obtained the results presented in the following table:

Table 01 : Age-specific distribution of diabetic patients.

Age	[20-30]	[30-40]	[40-50]	[50-60]	[60-70]	[70-80]	[80-90]	[90-100]
Number	20	37	59	128	150	80	15	21

We converted these table results to bar charts as shown below:

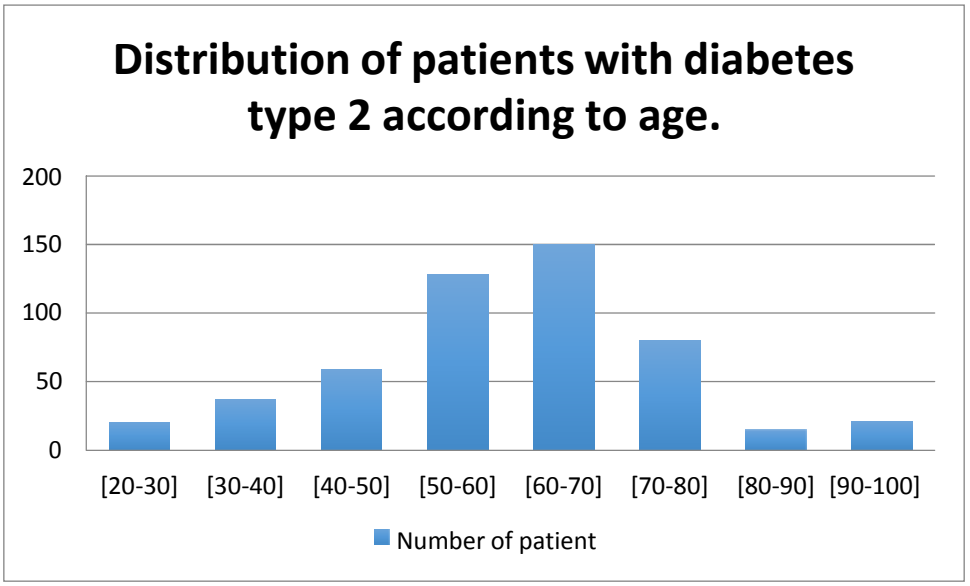


Figure 31: Distribution of patients with diabetes type 2 according to age.

Since the age of the subjects studied is between 20 and 100 years old, the most important age groups are [60-70] years old with a percentage of 29.41%, [50-60] years with a percentage of 25.10%, [70-80] years with a percentage of 15.69% and [40-50] years with a percentage of 11.57%.

The largest category is the female category, with a percentage of 69.41% an average of 354 women for 156 men.

For the adult population of Canada and the USA, the essential factor is a consequence of an advanced age pyramid (the proportion of the population over 50 years of age is expected to increase from 32% in 2010 to 36% in 2030) **(Shaw, Jonathan E et *al*, 2010)**

Diabetes is a major disease, affecting almost 14% of population between 75 and 80 years old

(Mohiuddin, A, 2019)

IV /1.3. Age and gender :

The development of type 2 diabetes does not depend on the age or the gender only; it can be linked to both at the same time. After examining the patient files, we obtained the results presented in the following table:

Table 02: distribution of patients type 2 diabetes by their age and gender.

	[20-30]	[30-40]	[40-50]	[50-60]	[60-70]	[70-80]	[80-90]	[90-100]	total
womens	13	20	34	100	110	56	10	11	354
P (%)	3,67%	5,64%	9,60%	28,24%	31,07%	15,81%	2,82%	3,10%	99,95%
men	7	17	25	28	40	24	5	10	156
P (%)	4,48%	10,89%	16,02%	17,94%	25,64%	15,38%	3,20%	6,41%	99,96%

To make the results obtained clearer, we have drawn the graph below:

	[20-30]	[30-40]	[40-50]	[50-60]	[60-70]	[70-80]	[80-90]	[90-100]
women	3,67%	5,64%	9,60%	28,24%	31,07%	15,81%	2,82%	3,10%
men	4,48%	10,89%	16,02%	17,94%	25,64%	15,38%	3,20%	6,41%

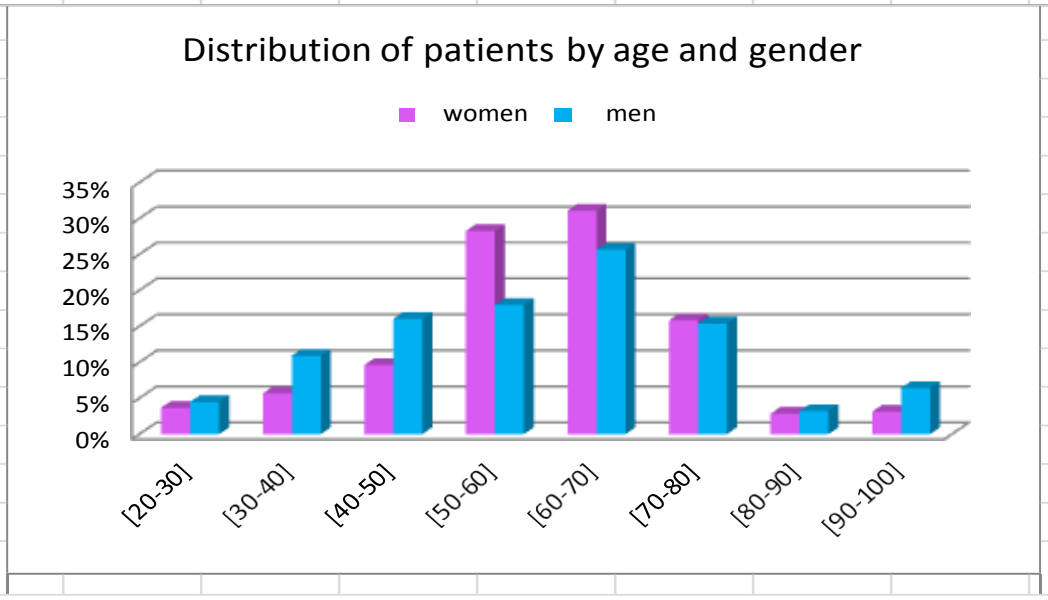


Figure 32 : Distribution of patients with diabetes type 2 according to age and gender.

After analyzing the data obtained, it was found that the female category is the most vulnerable to the disease. Compared to the male group. While women between the ages of 50 and 70 are the most vulnerable, with a rate of 75.12% with a rate of 266 women out of 354, while the age specified for men is between 40 and 70, with a rate of 74.98%, with a rate of 117 out of 156 men.

It also appears that the age between [60-70] is the stage when the number of people infected is higher than usual.

The overall prevalence of diabetes was 6.5% (95%CI: 5.4–7.6) and 6.4% (95%CI: 5.0–7.8) and 6.6% (95%CI: 4.8–8.4) among men and women correspondingly **(Nshisso, Lemba D, et *al*, 2012)**

IV /1.4. BMI and gender :

We measured the height and weight of all patients who consult the hospital in order to calculate BMI. The following table represents the distribution of patients according to their BMI:

Table 03 : the calculations of BMI"s type 2 diabetic patients.

BMI	N° women	N° men	total	P (%) wom	P (%) men
less than 18,5	20	1	21	5,64%	0,64%
[18,5-25[normal	64	18	82	18,07%	11,53%
[25-30[overweight	75	63	138	21,18%	40,38%
[30-35[moderate obesity	99	41	140	27,96%	26,28%
[35-40[severe obesity	86	26	112	24,29%	16,66%
more than 40 morbid obesity	10	7	17	2,82%	4,48%

BMI	P (%) women	P (%) men
less than 18,5	5,64%	0,64%
[18,5-25[normal	18,07%	11,53%
[25-30[overweight	21,18%	40,38%
[30-35[moderate obesity	27,96%	26,28%
[35-40[severe obesity	24,29%	16,66%
more than 40 morbid obesity	2,82%	4,48%

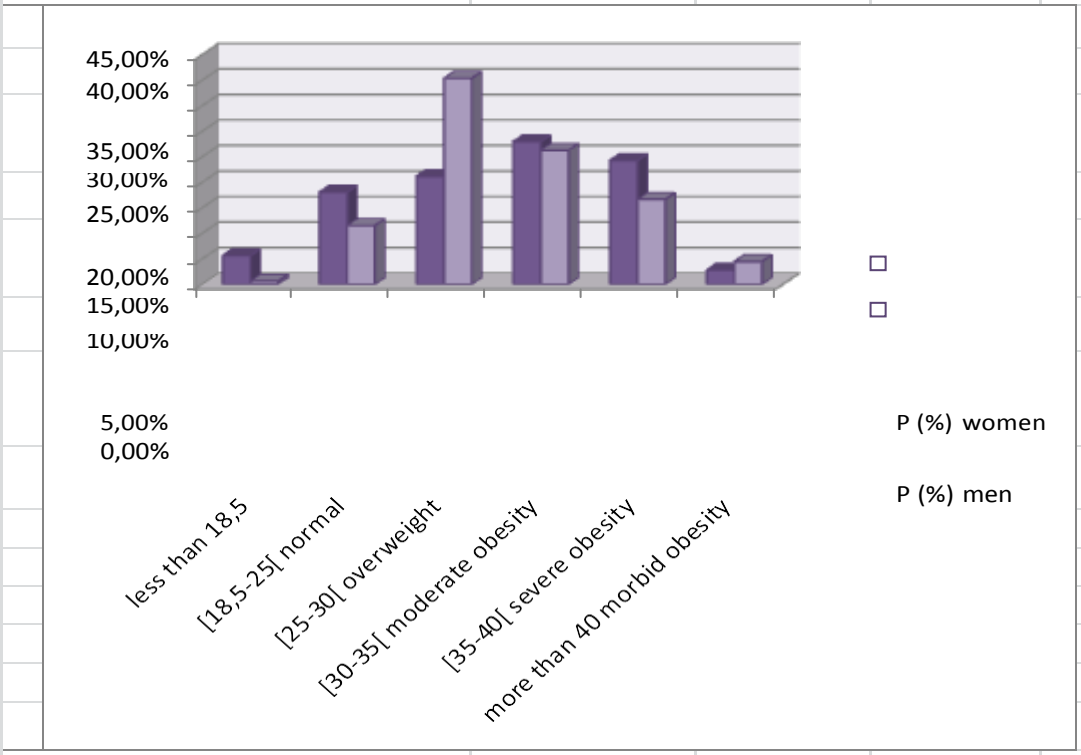


Figure 33: Distribution of patients with diabetes type 2 according to BMI.

The table and figure 33 above shows that the percentages of overweight women and women who have reduced obesity higher compared to that of women who have normal weight and who have severe obesity lean women a low percentage of patients.
Compared to males, the percentage of men was overweight and had a higher normal weight compared to that of women who moderately or severely obese however, the percentage of morbidly obese men lifted or is mobilins.

In a random study conducted in the communities of the districts of Kampala and Mokono, the prevalence of type 2 diabetes was found to be about 8.1% (*n* = 148). An association between obesity, hypertension, and risk of type 2 diabetes was found among the women, of whom nearly 80% were overweight. However, the men, who were primarily lean, did not exhibit this same correlation **(Lasky, David, et *al*, 2002)**

Body mass index **(BMI)**, weight gain and abdominal fat location are major risk factors for type 2 diabetes **(FOUDI, Lyes, 2017)**.

IV /2. The familial nature of diabetes :

familial diabetes prevalence	yes	no
percentage (%)	53%	47%

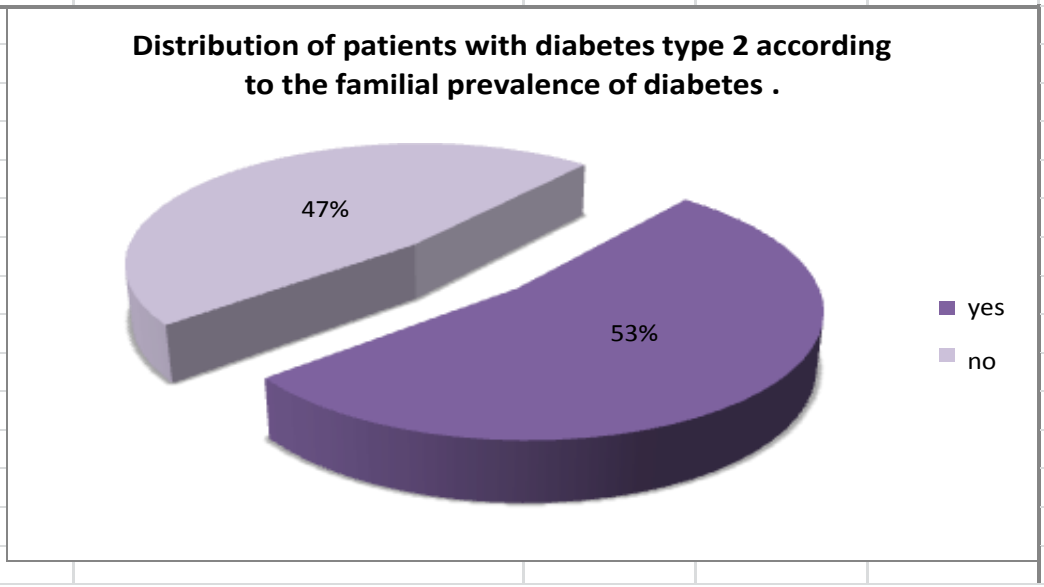


Figure 34: Distribution of patients with diabetes type 2 according to the familial prevalence of diabetes.

We found that most of the people with diabetes in our study also have family members who have diabetes. This means that having family members with diabetes increases a person's risk of also having diabetes.

It is estimated that the risk of developing diabetes is about 30% if you have a diabetic parent and approaches 70% if both parents are diabetic. A family history of diabetes is therefore a major risk factor for develop the disease **(Fery, Françoise et *al*, 2005)**

A 2007 survey in the Tlemcen region showed that more than 50% of people with diabetes had at least one family member with the disease **(Boutayeb, Abdesslam, et *al*, 2014)**

Numerous observations, in animal models and in the human species, show that fetal programming is capable of influencing the capital of B cells and, ultimately, to lead to development of T2DM in adulthood. Epigenetics contributes to the transgenerational transmission of T2D and offers, from this point of view, certain perspectives in terms of prevention of the disease.

IV /3. Lifestyle :

IV /3.1. Feeding :

We asked people questions about what they eat, and we made a picture to show the answers. This is called a bar chart or a histogram below:

feeding mood	frequency of fat gain	frequency of sugar intake fast	mediteranian food	junk food
yes	97	89	45	24
no	33	56	68	98

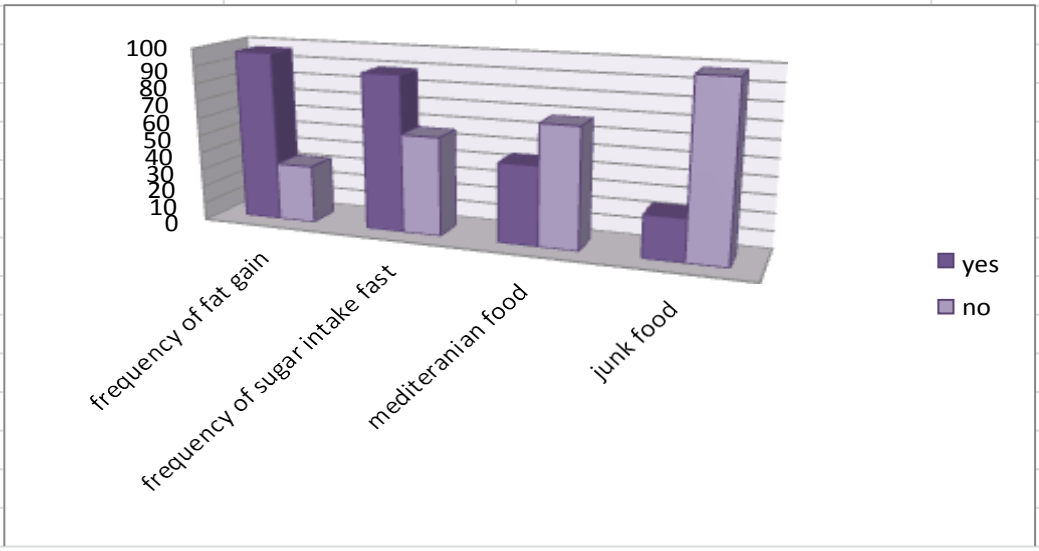


Figure 35: distrubition of patients according to their feeding mood.

People eat too much sugar and fat and don't always follow the instructions of the person who tells them what to eat. They also don't eat at the right times or eat the right amount of food during the day.

National Center for Health Statistics reported that socioeconomic status plays an important role in the development of T2DM; where it was known as a disease of the rich.49 On the contrary, the same reference reported that T2DM was more prevalent in lower income level and in those with less education. The differences may be due to the type of food consumed. Nutritionists advised that nutrition is very important in managing diabetes, not only type but also quantity of food which influences blood sugar. Meals should be consumed at regular times with low fat and high fiber contents including a limited amount of carbohydrates. It was observed that daily consumption of protein, fat and energy intake by Saudi residents were higher than what is recommended by the International Nutritional Organization **(Sami, Waqas, et *al*, 2017)**

Food contains essential elements for the proper functioning of the body: proteins, lipids (fats) and carbohydrates (food sugars). The most important thing is to limit the consumption of fatty foods to control the weight: oil, butter, cheese, cold meats, etc. Obesity is a leading cause of diabetes in a certain area. When you gain weight, your blood sugar rises, in case of overload, a diet allows you to improve or even correct your blood sugar. Carbohydrate-rich food during the day has a direct effect on blood sugar. Therefore, high consumption of carbohydrates causes hyperglycemia. The lack of carbohydrates during meals can lead to nutritional imbalances, sometimes even hypoglycemia if the treatment is too strong, so you should discuss this with your doctor.

IV /3.2. Tobacco :

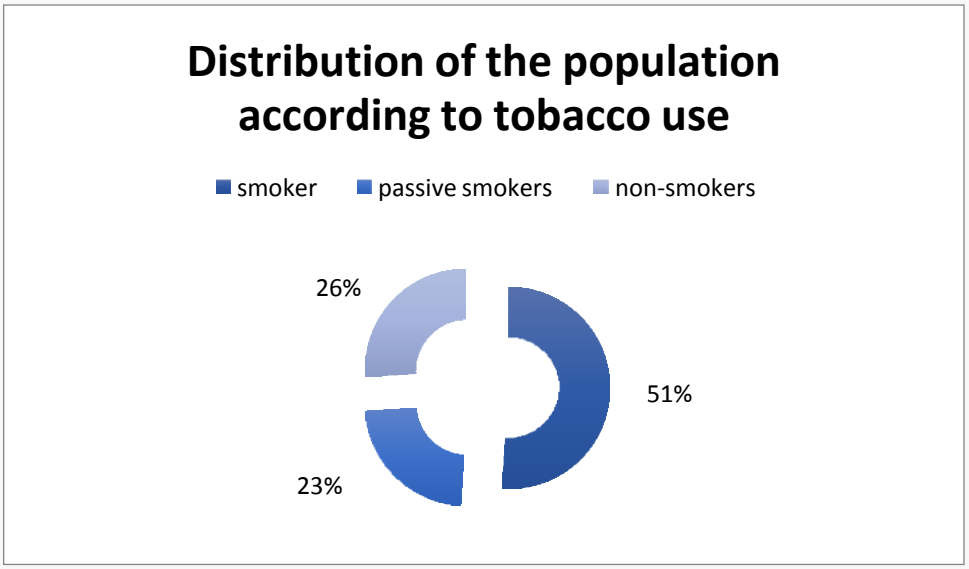


Figure 36: Distribution of the population according to tobacco use.

Most people who worked didn't smoke. Only a small number of men with diabetes smoked, and even fewer smoked without smoking themselves. No women were reported as smoking, but that does not mean that none of them smoke.

Smoking cessation may cause excessive weight gain in some individuals and may be associated with clinically significant outcomes such as diabetes or obesity. Interventions combining smoking cessation and weight management may be effective in improving smoking cessation and minimizing weight gain, but need to be tested in specific populations.

Periodontitis was present in 372 (71.3%), diabetes in 33 (6.3%) and smoking in 138 (26.4%). Hypertension was detected in 64 (12.3%) patients and diabetes in the family in 94 (18%). Among 372 patients with periodontitis, smoking behavior was present in 120 (32.3%), diabetes in 32 (8.6%), family history of diabetes in 72 (19.4%) and hypertension in 62 (16.7%). In contrast, 120 (87%) smokers, 33 (97%) diabetics, 72 (76.6%) family history of diabetes, 62 (96.9%) hypertension, 216 (41.4%) men and 156 (29.9%) women had periodontitis. Men had more smoking behavior: 115 (39.4%) compared to women 23 (10%)

(Gupta, Sujaya, et *al*, 2018)

IV/3.3. Physical activity :

s of patients	sporty	non-sporty	passive sporty
women	65	209	80
men	70	35	51
total	135	244	131

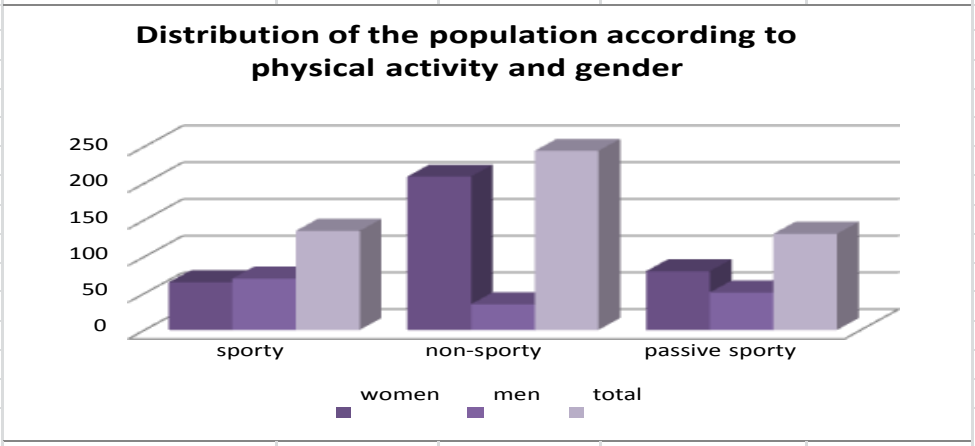


Figure 37: Distribution of the population according to physical activity and gender.

Most people with diabetes do not exercise, especially women. Even though exercise can help reduce weight and diabetes, only a small number of people with diabetes actually do it.

Several recent studies in humans an adverse association between objectively measured sitting and cardiometabolic risk factors such as HbA1c, central obesity, BMI, fasting triglycerides, systolic blood pressure, C-reactive protein and hyperglycemia has been observed in diabetic patients. Studies in people with and without type 2 diabetes have shown that interrupting sitting for light walking or light resistance exercise can reduce postprandial hyperglycemia and increases in insulin and triglyceride levels **(Pavithran, Nivedita, et *al*, 2020)**

Regular and moderate physical activity has a beneficial effect on longevity, reducing general mortality and especially cardiovascular mortality. Initial epidemiological data reported in the 1980s among former Harvard students were strongly supported by several studies conducted in large and diverse populations of men and women of various ages. It is generally accepted that physical activity **(PA)** plays a protective role against obesity. However, it is important to combine an appropriate low-calorie diet. In addition, physical activity favorably affects the distribution of fat, especially visceral fat, and increases muscle mass. The contribution of bodybuilding type exercises is interesting. The personal health benefits of regular exercise are still largely underestimated, while studies have shown that the practice can reduce mortality by 10% over seven years, especially cardiovascular mortality.

IV /3.4. Relationship between BMI and physical activity :

BMI	sporty women	non-sporty women	sporty men	non-sporty men
less than 18,5	0	0	0	0
[18,5-25[normal	15	29	13	26
[25-30[overweight	45	69	15	30
[30-35[moderate obesity	34	97	29	17
[35-40[severe obesity	12	49	10	16
more than 40 morbid obesity	0	4	0	0

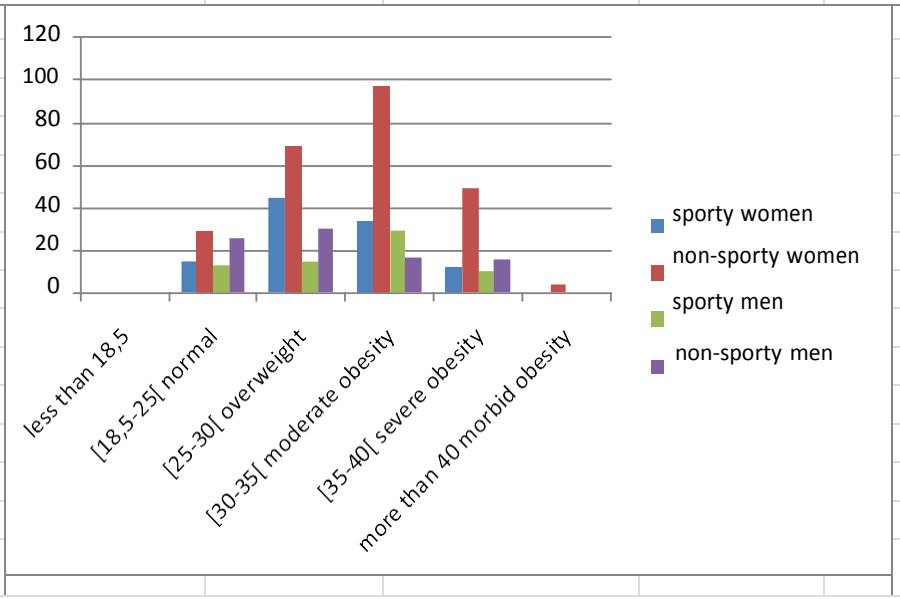


Figure 38: Relationship between BMI and physical activity.

The photo shows that some women are overweight because they don't exercise enough. It may be because they are not used to exercising and they sit too much. But men are not as affected by being overweight. It may be because they are more active.

In multivariate logistic regression analysis, the lowest quintile of BMI and the highest quintile of imageO2max were inversely associated with severe periodontitis, respectively. Patients with the lowest quintile of BMI and highest quintile of imageO2max had a significantly lower risk of severe periodontitis compared with patients with other combined quintiles of BMI and imageO2max (odds ratio: 0.17; 95% Confidence interval: 0.05 to 0.55) **(Shimazaki, Yoshihiro, et *al*, 2010)**

Activity-related energy expenditure increased with increasing body mass index, while mean physical activity levels were unchanged. Most obese subjects were moderately active. Increasing activity levels in obese subjects is limited by the ability to perform higher intensity exercise. Exercise programs that can handle overweight individuals have yet to achieve weight loss results. Any loss in fat mass is compensated by a gain in lean body mass **(Westerterp, K, R, 1999)**

IV /4. Distribution of the population according to associated pathologies :

Age	[20-30]	[30-40]	[40-50]	[50-60]	[60-70]	[70-80]	[80-90]	[90-100]
HTA	12	20	25	32	36	10	5	9
Dysfonction thyroïdian	16	22	26	11	8	0	0	0
Underlying cardiac pathologies	5	2	12	9	1	0	0	0
Dyslipidemia	30	8	11	12	20	0	0	0
Cancer	5	25	14	12	5	0	0	0
Corona	2	5	19	23	28	15	0	0

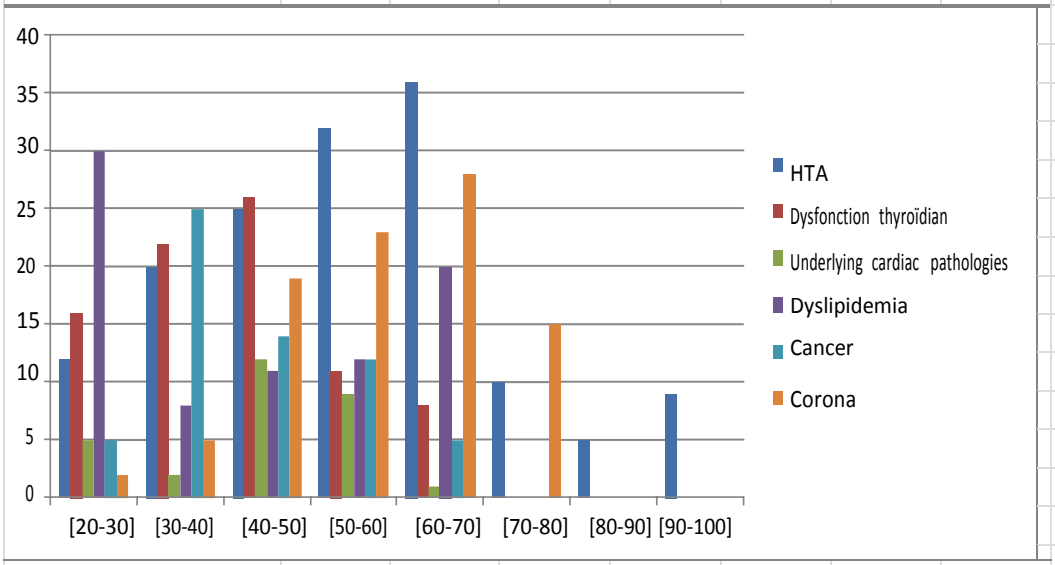


Figure 39: distrubition of the population according to pathologies.

Analysis of the data from our survey shows that 140 of the hypertensive subjects 28 %.

When a person has diabetes, they often have high blood pressure for many different reasons, such as not eating a healthy diet, not moving enough, being overweight and feeling stressed every day.

Mean age: 58 years (61-65 years), sex ratio: 4.8, type 2 diabetes: 132 (60.5%). His median duration of diabetes was 8.4 years, and 86% of patients had persistent imbalances. Degenerative complications identified in our patients: coronary syndrome (13.7%), AMI (12.3%), stroke (7.7%), retinopathy (9.6%), nephropathy (12.8%). All patients had at least one cardiovascular risk factor.

Type of hypertension: isolated systolic in 18% of cases. Hypertension classification: grade I (30%), grade II (45%), grade III (25%). Treatment: IEC was the most commonly prescribed antihypertensive agent in our series, accounting for 56% of mono-therapies, 25% of dual therapies, and 18% of triple therapies **(Filali, K et *al*, 2009)**

29 diabetic had underlying cardiac pathologies with 5,8% . 83 patients with 16,6%.

According to three studies conducted in order to find out the relationship between underlying Cardiac Conditions and Type 2 Diabetes show that the ACCORD study (Actions to Control Cardiovascular Risk in Diabetes) was terminated prematurely due to increased cardiovascular

and all-cause mortality (+22%) in the intensive care arm. Additional analyzes also showed that the observed increased cardiovascular mortality in the intensive care group was not associated with rapid improvement in glycemic control during the first months of the intervention.

In the **ADVANCE** study (Actions on Diabetes and Vascular Disease: A Controlled Release Review of Preterax and Diamicron), the association between the occurrence of severe hypoglycemia and the risk of complications Cardiovascular events and deaths were also found, again similar in patients in the intensive and standard groups.

A recent meta-analysis, based on 6 observational or interventional studies with a total of 903,510 subjects, confirmed an association between severe hypoglycemia and cardiovascular events with a relative risk of 2, 05 (75% CI: 1. 74-2. 42; $p<0.001$).

Despite the increased risk of hypoglycaemia, meta-analyses including some of these showed a significant reduction in the rates of non-fatal myocardial infarction and coronary events (approximately 15 %) was associated with improved glycemic control without affecting total mortality. Additional analyzes also showed that the increase in cardiovascular mortality observed in the intensive care group was not related to the rapid improvement in glycemic control during the first months of the intervention.

Indeed, in a population of more than 12,000 dysglycemic subjects at high cardiovascular risk, the occurrence of severe hypoglycaemia was associated with a significant risk excess for the composite endpoint **(ADVANCE Collaborative Group, 2008)**

Out of 500 people with diabetes, 81 patients of them had a problem with their cholesterol levels 16,2%.

In this way, the low HDL-C levels associated with hyperinsulinemia or insulin resistance and insulin signaling for insulin-mediated glucose clearance are characterized by plasma glucose and fasting insulin concentrations. Thus, in dyslipidemia, the use of lipoprotein concentration ratios is associated with insulin resistance and increased risk of cardiovascular disease.

Then, these major changes associated with the insulin resistance syndrome are increased TGRLs and decreased HDL-C levels. Obesity, metabolic syndrome, and T2DM may also show the same dyslipidemia characteristic and measuring TG, HDL-C, TC/HDL-C and TG/HDL-C ratio in circulation may also use as insulin resistance estimation **(Tangvarasittichai, Surapon, 2015)**

IV/5. Individual treatment of type 2 diabetes :

IV/5.1.Population distribution according to the deit; immediate medication and alternative treatment :

patients	immediate treatment	after a diet
yes	356	356
no	154	154

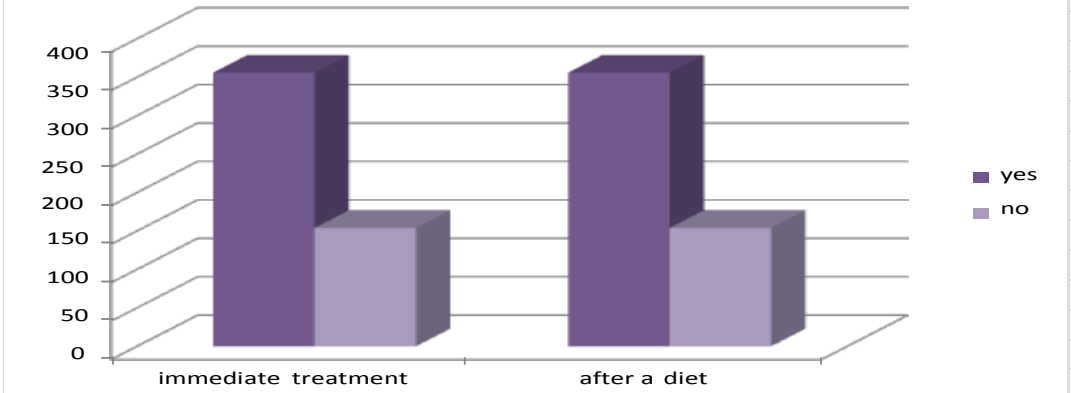


Figure 40: Population distribution according to the deit; immediate medication and alternative treatment.

Before taking diabetes medication, it is important to eat healthy foods and exercise to maintain normal blood sugar levels and avoid falling too low or too high. It can also help prevent problems that may arise if you take medication for a long time. Eating less and losing weight can also help prevent diabetes.

Current treatment of type 2 diabetes focuses on pharmacotherapy and a high-carbohydrate diet, but the ketogenic diet is an effective alternative that is less dependent on drugs and even a preferred option when drugs are not available **(Westman, Eric C, et *al,* 2018)**

The results suggest that regular exercise is a good way to promote glycemic control in people with type 2 diabetes, but all these studies were at high risk of bias.

IV/5.2. Distribution of patients by age of diabetes :

age of diabetes	[0-10[	[10-20[	[20-30[	[30-40[	[40-50[	[50-60[
number of patients	75	145	96	78	55	61

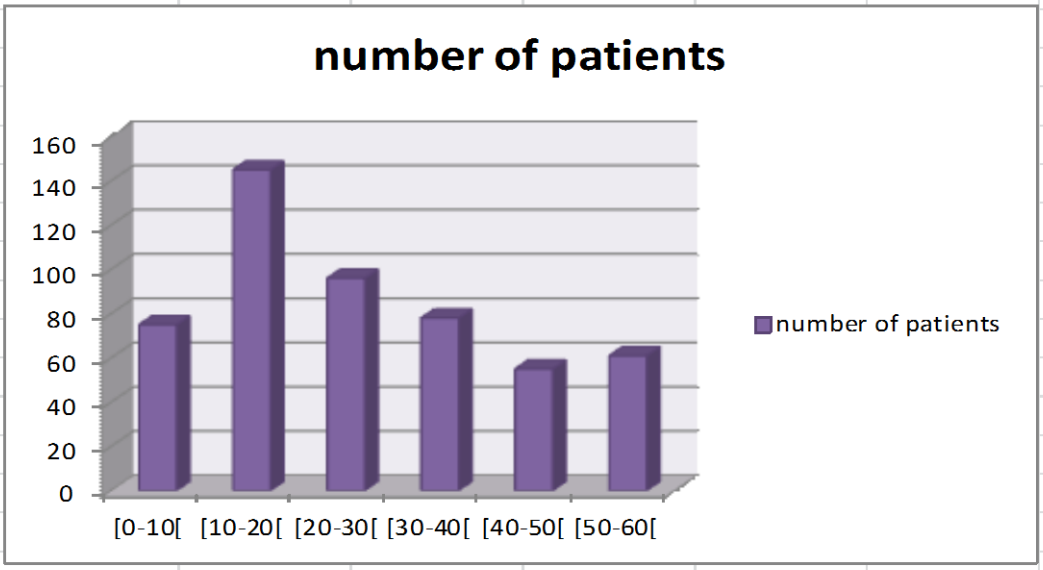


Figure 41: Population distribution according to the age of diabetes.

We looked at how long people had diabetes and organized the information in a certain way. We obtain the following results:

- ✓ 75 patients 14.70% had an age of diabetes between 0 to 10 years.
- ✓ 145 patients 28.43% had an age of diabetes between 10 to 20 years.
- ✓ 96 patients 18.82% had an age of diabetes between 20 to 30 years.
- ✓ 78 patients 15.29% had an age of diabetes between 30 to 40 years.
- ✓ 55 patients 10.78% had an age of diabetes between 40 to 50 years.
- ✓ 61 patients 11.96% had an age of diabetes between 50 to 60 years.

Most of the people we studied had diabetes for 0-20 years, but some had it for up to 30 years. Diabetes is a disease that needs to be watched carefully for a long time, and most people have taken good care of it.

In an alternative study found that the mean duration of diabetes was numerically longer in group II (11.63 ± 5.9 years) than in group I (8.23 ± 5.54 years) **(Alavudeen, Sirajudeen Shaik, et *al*, 2020)**

Another study conducted that factors found to be associated with quality of life in patients with hypoglycaemia included having an educational level of senior high school or above, being on an insulin regimen only, engaging in regular exercise, diabetes complications, fear of hypoglycaemia and greater social support, which accounted for 28.5% of the total variance. **(Huang, Mei-Chuan, et *al*, 2020)**

IV/5.3. Distribution of the population by type of antidiabetic treatment :

treatement	oral antidiabetic	oral antidiabetic + insulin	insulin only
number of patients	65%	20%	15%

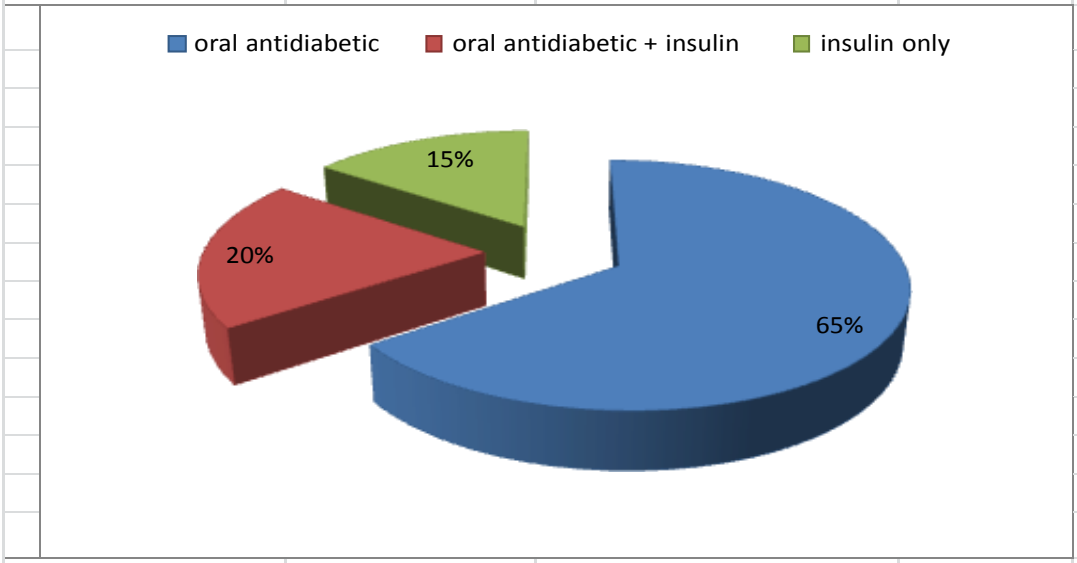


Figure 42: Distribution of the population according to the treatment of type 2 diabetes.

Most patients were taking oral diabetes medication, about 65%. Some took insulin, which is another type of medicine, about 15%. And some took both types of drugs at the same time, about 20%.

The main classes of oral antidiabetic drugs include biguanides, sulfonylureas, meglitinides, thiazolidinediones **(TZDs)**, dipeptidyl peptidase 4 **(DPP-4)** inhibitors, sodium glucose cotransporter **(SGLT2)** inhibitors, and α-glucosidase Includes inhibitors **(Chaudhury, Arun, et *al*, 2017)**

Use of the drug as monotherapy corresponds to the most common treatment regimen, with most patients receiving metformin monotherapy, and these results are similar to those reported in the literature **(Inoue, Hiroyuki, et *al*, 2019)**

IV/6. Obesity and fatty liver disease :

Obesity is a big problem all over the world and is caused by many factors like genetics, environment and habits. Being obese can also make your liver too fatty, which can be a serious problem that you might not even know about until it gets really bad. This can lead to very serious diseases like liver cancer. We'll talk about the causes of obesity and fatty liver disease, how to tell if you have them, and how to treat them.

Obesity is associated with an increased risk of non-alcoholic fatty liver disease **(NAFLD).** The relationship between **BMI** and **NAFLD** is influenced by racial/ethnic background and genetic variation in specific genes **(Sherif, Zaki A, et *al*, 2016)**

Non-heavy drinking might not reduce the risk of **CVD** in **NAFLD** subjects. On the contrary, even moderate drinking could promote hepatic fibrosis. Thus**, NAFLD** drinkers should not be recommended for even a moderate amount of alcohol **(Kashiwagi, Kazuhiro, et *al*, 2020)**

Fatty liver is closely related to obesity. This relationship is based on the fact that obesity leads to a significant enlargement of intra-abdominal visceral fat deposits **(Polyzos, Stergios A et *al*, 2019)**

IV/6.1. Diabetes and fatty liver disease :

Diabetes and fatty liver disease are two diseases that often occur together. Fatty liver disease occurs when too much fat builds up in your liver, which can damage it and make it malfunction. This can lead to serious liver problems. Diabetes is a disease that prevents your body from controlling the amount of sugar in your blood. There are two types of fatty liver disease: one is caused by excessive alcohol consumption and the other is related to being overweight or insulin problems, which can also lead to diabetes.

NAFLD is very common in people with type 2 diabetes and is associated with a high prevalence of CVD **(Targher, Giovanni, et *al*, 2007)**

Patients with NAFLD and DM are at risk of developing aggressive outcomes such as cirrhosis and death **(Younossi, Zobair M, et *al*, 2004)**

The presence of both NAFLD and T2DM not only increases the likelihood of developing diabetic complications (including both macrovascular and microvascular complications), but also more serious complications, including cirrhosis, hepatocellular carcinoma, and death **(Mikolasevic, I, et *al*, 2021).** Nonalcoholic fatty liver disease **(NAFLD)** and type 2 diabetes mellitus **(T2DM)** often coexist because they share the pathogenic abnormalities of excessive obesity and insulin resistance **(Smith, Briohny W et *al*, 2011)**

IV/7. Potential role of sugar (fructose) in the epidemic of obesity and diabetes:

Many people have problems with being overweight and contracting a disease called diabetes. One thing that can make these problems worse is a type of sugar called fructose. Fructose is found in some foods and beverages, and is also added to others to make them taste sweet. In this lecture, we will learn more about how fructose can affect our body and make us unhealthy.

There is a study concluded that Fructose intake is a risk factor for hypertension, insulin resistance, hypertriacylglycerolemia, obesity, type 2 diabetes, preeclampsia, and chronic kidney disease. Concentration, body weight, reduces the risk of progression of kidney disease, and reduces the risk of cardiovascular disease. Fourth, fructokinase has been identified as a key enzyme that mediates cardiovascular disease syndromes. Genetic polymorphisms are associated with cardiovascular disease risk, and blocking the enzyme offers a new way to prevent cardiovascular disease **(Johnson, Richard J, et *al*, 2007)**

IV/ 7.1. Influence of high fructose on obesity : body weight, body fat and TG levels :

Eating too much high fructose corn syrup can make a person gain weight and fat and can cause problems with their body. This is because the body processes it differently than other sugars and it has a lot of calories. To stay healthy, it's important to limit how much high fructose corn syrup we eat and choose healthier foods. By doing this, we can stay healthy and avoid getting sick.

NALFD patients had a higher energy intake with a significantly higher glucose and protein consumption and a lower fiber and mineral consumption per 1000 kcal. However, no significant differences regarding carbohydrates, fructose and fat per 1000 kcal energy intake were appreciated **(Perdomo, Carolina M et *al*, 2019)**

Some studies have shown that short-term access to **HFCS** can lead to weight gain, but the results are mixed. The current study examined the short-term and long-term effects of **HFCS** on body weight, body fat and circulating triglycerides. Experiment 2 investigated the long-term effects of **HFCS** on weight and obesity parameters and gender differences. Over the course of 6 or 7 months, both male and female rats given access to **HFCS** gained significantly more weight than controls. This HFCS-induced increase in body weight was accompanied by an increase in adipose fat, especially in the abdomen, and an increase in circulating levels of triglycerides **(Bocarsly, Miriam E, et *al*, 2010)**

IV/ 7.2. Fructose and the Insulin-resistance :

Fructose is a type of sugar that is found naturally in fruits and honey, and is also commonly used as a sweetener in processed foods and beverages. While fructose is often touted as a healthier alternative to other types of sugar, research suggests that consuming high amounts of fructose may contribute to insulin resistance.

Insulin resistance is a condition in which the body's cells become less responsive to insulin, a hormone that helps regulate blood sugar levels. When the body becomes insulin resistant, the pancreas must produce more insulin to keep blood sugar levels in check. Over time, this can lead to high blood sugar levels and an increased risk of type 2 diabetes.

One way that fructose may contribute to insulin resistance is by increasing the production of fat in the liver. When fructose is consumed in large amounts, it is converted into fat in the liver, which can lead to a condition known as non-alcoholic fatty liver disease (NAFLD). NAFLD has been linked to insulin resistance and an increased risk of type 2 diabetes.

Additionally, fructose may also contribute to insulin resistance by disrupting the normal functioning of insulin signaling pathways in the body. Research has shown that consuming high amounts of fructose can lead to changes in the way that insulin receptors function, which can impair the body's ability to respond to insulin.

Overall, while fructose can be a part of a healthy diet in moderation, consuming high amounts

of fructose may contribute to insulin resistance and an increased risk of type 2 diabetes. It is important to limit intake of added sugars, including fructose, and to focus on a diet rich in whole, unprocessed foods to support overall health and well-being.

Excessive caloric intake from a high-fat diet **(HFD)** has long been recognized as a major risk factor for developing obesity and its complications, such as fatty liver disease and insulin resistance. In summary, dietary fructose intake strongly promotes hepatic insulin resistance through a complex interplay of multiple metabolic pathways.

Current evidence indicates that fructose, but not glucose causes metabolic complications, contradicting the idea that fructose is merely a source of delicious calories that lead to weight gain and increased insulin resistance **(Lara-Castro, Cristina et *al*, 2004)**

Certain metabolic differences exist between glucose and fructose, and the results that were once thought favorable, proved exacerbating to insulin resistance and obesity.

Increasingly, the question is being raised whether dietary carbohydrate and fructose intake is directly related to the development of type 2 diabetes. As insulin resistance is commonly associated with circulating C-peptide concentrations, a cross-sectional study was conducted to assess fructose, carbohydrate, and glycemic load in relation to dietary C-peptide concentrations. The highest quintile of fructose intake was found to have 13.6% lower levels of his C-peptide, suggesting that these types of nutrients may play opposing roles in the development of insulin resistance. Homocysteine was found to be higher in patients with stenotic vessels and coronary artery disease, and indeed highest in diabetics.

It involves GLUT5, a fructose transporter with significantly higher expression levels in young obese ***Zucker*** rats compared to lean controls. As rats age and become diabetic, GLUT5 abundance and activity are impaired, causing more pronounced insulin resistance compared with lean rats, and the pathology of metabolic syndrome associated with fructose feeding and insulin resistance. Suggesting a possible role for his GLUT5 receptor in rats fed 66% fructose for 2 weeks, insulin receptor mRNA and subsequent numbers of insulin receptors in skeletal muscle and liver were significantly increased compared to standard chow-fed rats. Although substrate (IRS) protein levels were similar, insulin-induced IRS (1/2) phosphorylation was significantly reduced in both liver and muscle of fructose-fed rats **(Walker, Celia G, et *al*, 2007)**

CONCLUSION

Conclusion :

Diabetes type 2 is a chronic condition in which the body either does not produce enough insulin or is unable to use it effectively. Insulin is a hormone that helps regulate blood sugar levels. In type 2 diabetes, the body becomes resistant to insulin, which causes blood sugar levels to rise. This can lead to a range of health problems, including heart disease, kidney damage, nerve damage, and blindness. Type 2 diabetes is often associated with obesity and a sedentary lifestyle, and can be managed with lifestyle changes, medication, and insulin therapy.

Obesity is a medical condition characterized by excessive body fat accumulation that can lead to negative health effects. It is typically defined as having a body mass index **(BMI)** of 30 or higher. Obesity is caused by a combination of genetic, environmental, and lifestyle factors, including overeating, lack of physical activity, and genetics. Obesity can lead to a range of health problems, including type 2 diabetes, heart disease, high blood pressure, stroke, sleep apnea, and certain types of cancer. Treatment for obesity typically involves lifestyle changes such as diet and exercise, as well as medication and in some cases, surgery.

Diabesity is a term used to describe the close relationship between diabetes and obesity. It is a growing health concern worldwide due to its rising prevalence and associated health risks. The link between diabetes and obesity is complex, with both conditions influencing each other. Obesity increases the risk of developing type 2 diabetes, while diabetes can lead to weight gain and further complications.

NAFLD is the most common chronic liver diseases. It encompasses a broad spectrum of histological entities and is considered to be the hepatic manifestation of the syndrome metabolic (SM). NAFLD and its more severe form, non-alcoholic steatohepatitis (NASH) whose complications can lead to cirrhosis and hepatocellular carcinoma (HCC). Obesity, dyslipidemia, type 2 diabetes and insulin resistance (IR) are important NAFLD risk factors. Estimating these factors therefore makes it possible to predict the risks of NAFLD

Our epidemiological studies found that 510 type II diabetics at the level of the hospital in wilaya of Naama identified a significantly increased prevalence of T2D in the female-dominated Naama area. Association with multiple factors, including gender, older age, obesity, and family history of disease. The majority of patients have diabetes, arterial hypertension, retinopathy, plus the most common comorbidities. Analysis of glucoregulatory status (blood glucose and her Hba1c) shows that the patient has a blood glucose imbalance.

This investigation is still preliminary and superficial and requires further investigation.

Thoroughly, the idea after this work is to continue to follow the patient in the future, establish tight glycemic control with everything that entails (diet, physical activity, etc.), and even if it comes to one. To worsen or stabilize blood sugar profile comes to avoid all the complications we encountered during the study.

REFERENCES

References :

- **Boyarkine, C.** L'Organisation mondiale de la santé et le Règlement sanitaire international (2021)
- **REDJEM, Mayar, and Sarab DOUICHINE.** *Maladies et complications associées au Diabète type 2*. Diss. Université Larbi Tébessi-Tébessa, (2022).
- **Tenenbaum, Mathie, et *al*.** "Physiopathologie du diabète." Revue francophone des laboratoires 2018.502 (2018): 26-32.
- **RYAD, BOUABDALLAH, and BOUABDALLAH RAZIA FAIZA.** *Etude de l'obésité et des altérations métaboliques chez les diabétiques de type 2 sous Metformine de la wilaya de Tlemcen*. Diss (2020).
- **Bauduceau, Bernard, and Lyse Bordier.** "Le diabète." Solar, (2017).
- **Nemi, Komi Dzidzonu, et *al*.** "Les modes de révélation du diabète sucré au CHU Sylvanus Olympio de Lomé." *The Pan African Medical Journal* 34 (2019).
- **("IDF DIABETES ATLAS" (**2019)
- **Dali-Sahi, M., et *al*.** "Type 2 dans des populations endogames de l'ouest algérien." *Leban Sci J* 13.2 (2012): 17.
- **Salemi, Ouassila**. "Pratiques alimentaires des diabétiques. Étude de quelques cas à Oran (Algérie)." *Économie rurale* 318.9 (2010): 80-95.
- **TOUATI, Rachida, et al.** *Etude épidémiologique de l'incidence du diabète de type II dans la wilaya de Médéa*. Diss.(2021.)
- **Punthakee, Zubin, Ronald Goldenberg, and Pamela Katz**. "Definition, classification and diagnosis of diabetes, prediabetes and metabolic syndrome." *Canadian journal of diabetes* 42 (2018): S10-S15.
- **Cheisson, Gaëlle, et *al*.** "Texte 1: rappels sur l'hyperglycémie." *Anesthésie & Réanimation* 3.3 (2017): 212-217.
- **mondiale de la Santé, Organisation**. "Rapport mondial sur le diabète." (2016).
- **Henri, E., et *al*.** "Place of Fructosamine in Gestational Diabetes Screening Strategy: Preliminary Study about 21 Cases at Laquintinie Hospital (Douala-Cameroon)." *Int J Gynecol Clin Pract* 7.155 (2020): 2.
- **MESSAAD, Wahiba, Chaima SOLTANI, and Hadil AMRI.** *Syndrome métabolique et diabète type II*. Diss. Université Larbi Tébessi-Tébessa, (2022).
- **NARIMENE, BOUHAIK, and BOUHAIK MANEL.** *interaction médicamenteuse chez les diabétiques de type 2 hypertendus sous metformine*. Diss.(2021)
- **BELFAR, Karima, and Hadjar BOUSSAADIA.** *Comparaison entre la médecine traditionnelle et la médecine moderne dans le traitement de certaines maladies*. Diss. UNIVERSITE MOHAMED BOUDIAF- M'SILA,(2020.)
- **Bessaguet, Flavien, and Alexis Desmoulière.** "Le pancréas." *Actualités Pharmaceutiques* 60.607 (2021): 55-59.
- **Longnecker, Daniel S.** "Anatomy and Histology of the Pancreas (version 1.0)." *Pancreapedia: The Exocrine Pancreas Knowledge Base* (2014).
- **Columbia University Irving Medical Center,** Department of Surgery, New York, NY(1999-2022)
- **Bouberka, Sarah, and Célia Bouguena.** *Synthèse bibliographique sur le diabète et sa physiopathologie*. Diss. Université Mouloud Mammeri, (2021).
- **Ahlem, Chiheb.** "L'adénocarcinome pancréatique et diabète: liens immuno-physiopathologiques."(2020)

- **Rick-Léonid Ngoua Meye Misso** Enquête épidémiologique du diabète et hypertension et plantes médicinales antidiabétiques et antihypertenseurs (2014)
- **Leung, P.S., Cheng, Q**. (2010).
- **Unson, C.G.** Glucagon and the Glucagon Receptor: Merrifield Years at the Interface of Chemistry and Biology. Int J Pept Res Ther 13, 19-27 (2007).
- **Doumbia, Abdou Karim.** "Evaluation des risques cardiovasculaires chez les patients diabétiques type 2 au CSRef de la commune II." (2019).
- **Spencer Sutton**. Science History Images / Alamy Banque D'Images
- **Mosbah, H., and F. Andreelli.** "Physiologie de la sécrétion d'insuline: Physiology of insulin secretion." *Médecine des maladies métaboliques* 6.3 (2012): 215-219.
- **C.Megan; A.Ktorza,** EMC-Endocrinologie (2005)
- **Capeau, Jacqueline.** "Voies de signalisation de l'insuline: mécanismes affectés dans l'insulino-résistance." *médecine/sciences* 19.8-9 (2003): 834-839.
- **Girard, J.** "Les actions physiologiques de l'insuline." *Médecine des maladies Métaboliques* 2 (2008): S124-S129.
- **Ruud, J. et *al.*** Neuronal control of peripheral insulin sensitivity and glucose metabolism. Nat. Commun. 8, 15259 doi: 10.1038/ncomms15259 (2017)
- **Lewis, Gary & Carpentier, André & Adeli, Khosrow & Giacca, Adria.** (2002). Disordered Fat Storage and Mobilization in the Pathogenesis of Insulin Resistance and Type 2 Diabetes. Endocrine reviews. 23. 201-29. 10.1210/edrv.23.2.0461.
- **Sophie Tesseraud, Sonia Métayer, Sophie Duchêne, Karine Bigot, Jean Grizard, Joëlle Dupont,**Regulation of protein metabolism by insulin: Value of different approaches and animal models,Domestic Animal Endocrinology,Volume 33, Issue 2,(2007),Pages 123-142,
- **Bougnères, Pierre, and Philippe Chanson.** "Récepteurs de l'insuline dans le cerveau, contrôle du poids et de la reproduction." *Médecine thérapeutique/Endocrinologie* 2.6 (2001).
- **Abimbola A. Akintola,** Department of Gerontology and Geriatrics, Leiden University Medical Center, C7-124,Albinusdreef 2, Leiden 2333 ZA,Netherlands(2015).
- **Milad Abdollahi, Sayyed Mohammad Marandi, Kamran Ghaedi, Zahra Safaeinejad, Fatemeh Kazeminasab, Samaneh Shirkhani, Mohammad Hossein Sanei, Parsa Rezvanian, Mohammad Hossein Nasr-Esfahani;** Oxidative Medicine and Cellular Longevity(2022)
- **L'ADA, E. T. L. O. M. S.** "Diagnostic et classification du diabète sucré les nouveaux critères." *Diabetes & Metabolism (Paris)* 25 (1999): 72-83.
- **Adouane Kenza, Semahi Nariman.** "Etude épidémiologique sur l'effet du diabète type 2 dans l'évolution de la maladie d'Alzheimer."(2021).
- **Lankatillake, Chintha & Huynh, Tien & Dias, Daniel.** (2019). Understanding glycaemic control and current approaches for screening antidiabetic natural products from evidence-based medicinal plants. Plant Methods. 10.1186/s13007-019-0487-8.
- **Rigalleau, V., J. Lang, and H. Gin.** "Étiologie et physiopathologie du diabète de type 2." *Endocrinologie-Nutrition* 10 (2007): 10-366.
- **Pylypchuk, George & Vincent, Lloyd & Wentworth, Joan & Kiss, Alexander & Perkins, Nancy & Hartman, Susan & Ironstand, Laurie & Hoppe, Jacqueline & Tobe, Sheldon.** (2008). Diabetes Risk Evaluation and Microalbuminuria (DREAM) studies: ten years of participatory research with a First Nation's home and Community Model for type 2 Diabetes Care in Northern Saskatchewan. International journal of

- **circumpolar health.** 67. 190-202. 10.3402/ijch.v67i2-3.18264.
- **Boirie, Y.** "Obésité: physiopathologie et conséquences." *Obésité morbide et urgences* 16 (2009).
- **SOUHILA, ZAHRAOUI, and MAMMAD SAKINA.** *Prévention de l'obésité par des micronutriments*. Diss.
- **Gremeaux, V., and B. Bouillet.** "Obésité, diabète de type 2, et activité physique." *La Lettre de médecinephysique et de réadaptation* 28.1 (2012): 3-11.
- **Prabha A, Devang N, Nandini M** (2018) Phenotypical Classification of Type 2 Diabetes Mellitus. J Endocrinol
- **Junquero, Didier, and Yves Rival**. "Syndrome métabolique: quelle définition pour quel (s) traitement (s)?." *médecine/sciences* 21.12 (2005): 1045-1053.
- **Salma, M. O. U. I. C. I., H. A. M. D. I. Sakina, and M. O. U. I. C. I. Hadjer.** *Syndrome métabolique et obésité: Etude épidémiologique et clinique à Tébessa*. Diss. Universite laarbi tebessi tebessa, 2020.
- **Scott M. Grundy,Metabolic Syndrome:** Connecting and Reconciling Cardiovascular and Diabetes Worlds,Journal of the American College of Cardiology,Volume 47, Issue 6,2006,Pages 1093-1100,
- **FOUDI, Lyes.** *DÉPISTAGE DU DIABÈTE SUCRÉ AU NIVEAU DE LA WILAYA DE BOUIRA*. Diss. Université de Bouira, 2017.
- **Ley, Sylvia & Korat, Andres & Sun, Qi & Tobias, Deirdre & Zhang, Cuilin & Qi, Lu & Willett, Walter & Manson, JoAnn & Hu, Frank. (**2016). Contribution of the Nurses' Health Studies to Uncovering Risk Factors for Type 2 Diabetes: Diet, Lifestyle, Biomarkers, and Genetics. American Journal of Public Health. 106. e1- e7. 10.2105/AJPH.2016.303314.
- **Duclos, M., C. Sanz, and J-F. Gautier.** "Activité physique et prévention du diabète de type 2." *Médecine des maladies métaboliques* 4.2 (2010): 147-151.
- **Feig, Denice S., et al.** "Diabète et grossesse." *Can J Diabetes* 42.3 (2018): S255-82.
- **Longmore, D.K., Barr, E.L.M., Wilson, A.N. et al.** Associations of gestational diabetes and type 2 diabetes during pregnancy with breastfeeding at hospital discharge and up to 6 months: the PANDORA study. Diabetologia 63, 2571-2581 (2020). https://doi.org/10.1007/s00125-020-05271-9
- **Clair, Carole, I. Berlin, and J. Cornuz.** "Tabagisme, obésité et diabète: une interaction cliniquement importante." *Revue médicale suisse* 319 (2011): 2338.
- **1.Śliwińska-Mossoń M, Milnerowicz H.** The impact of smoking on the development of diabetes and its complications. Diabetes and Vascular Disease Research. 2017;14(4):265-276. doi:10.1177/1479164117701876
- **KLAA, Fatma, and Djihed MENIA.** *La diversité alimentaire comme facteur de risque d'obésité chez les patients atteints de diabète type 2*. Diss. Université Larbi Tébessi-Tébessa, 2022.
- **Vors, C., et al.** "Intérêt de la phase postprandiale pour la santé de l'Homme." *Obésité* 9.1 (2014): 31-41
- **Hernandez, Angela, François R. Jornayvaz, and Jacques Philippe.** "Sommeil et diabète." *Rev Med Suisse* 8 (2012): 1198-203.
- **Ganamé, Yaya.** *Evaluation des facteurs de risque cardiovasculaire chez les patients diabétiques de type 2 hospitalisés dans le service de médecine et d'endocrinologie de l'hôpital du Mali*. Diss. USTTB, 2019.
- **Guillausseau, P-J., and M. Laloi-Michelin.** "Physiopathologie du diabète de type 2." *La revue de médecine interne* 24.11 (2003): 730-737.
- **Fery, Françoise, and Nicolas Paquot.** "Etiopathogénie et physiopathologie du diabète de type 2." *Revue Médicale de Liège* 60.5-6 (2005).

- **Rigalleau, V., J. Lang, and H. Gin.** "Étiologie et physiopathologie du diabète de type 2." *Endocrinologie-Nutrition* 10 (2007): 10-366.
- **DeFronzo, R. A.** "Insulin resistance, lipotoxicity, type 2 diabetes and atherosclerosis: the missing links. The Claude Bernard Lecture 2009." *Diabetologia* 53.7 (2010): 1270-1287.
- **De Luca, Carl, and Jerrold M. Olefsky**. "Inflammation and insulin resistance." *FEBS letters* 582.1 (2008): 97-105.
- **Schlienger, Jean-Louis.** "Type 2 diabetes complications." *Presse medicale (Paris, France: 1983)* 42.5 (2013): 839-848.
- **sriramakrishnahospital**
- **Diabetic Nephropathy | Diabetic** nephropathy, Basement membrane, Medical school life
- **Stout, Robert W.** "Diabetes and atherosclerosis." *Biomedicine & pharmacotherapy* 47.1 (1993): 1-2
- **Hamasaki, Hidetaka.** "Daily physical activity and type 2 diabetes: A review." *World journal of diabetes* 7.12 (2016): 243.
- **Forouhi, Nita G., et al.** "Dietary and nutritional approaches for prevention and management of type 2 diabetes." *Bmj* 361 (2018).
- **Scheen, A-J.** "Antidiabétiques oraux dans le traitement du diabète de type 2: perspectives historique et médico-économique." *Médecine des maladies Métaboliques* 9.2 (2015): 186-197
- **Mudaliar, Sunder, and Robert R. Henry.** "New oral therapies for type 2 diabetes mellitus: the glitazones or insulin sensitizers." *Annual review of medicine* 52.1 (2001): 239-257
- **Duclos, M., J. Ouennoughi, and S. Penando.** "P160 Effet hypoglycémiant des glinides au cours de
- **l'exercice musculaire chez les DT2."** *Diabetes & Metabolism* 36 (2010): A76.
- **Blicklé, J. F., E. Andres, and J. M. Brogard.** "Actualités dans les traitements du diabète de type 2. Les inhibiteurs des alpha-glucosidases." *La Revue de médecine interne* 20 (1999): 379s-383s.
- **Grira, W., et al.** "CA-123: L'insulinothérapie chez le diabétique type 2: en ambulatoire ou en hospitalisation?." *Diabetes & Metabolism* 42 (2016): A68.
- **Theintz, G.** "De l'obésité au diabètede." *Rev Med Suisse* 1 (2005): 477-80.
- **Haththotuwa, Rohana N., Chandrika N. Wijeyaratne, and Upul Senarath.** "Worldwide epidemic of obesity." *Obesity and obstetrics*. Elsevier, 2020. 3-8.
- **Evan L. O'Keefe, James J. DiNicolantonio, Harshal Patil, John H. Helzberg,**

  Carl J. Lavie, Lifestyle Choices Fuel Epidemics of Diabetes and Cardiovascular

  Disease Among Asian Indians,
- **Progress in Cardiovascular Diseases,** Volume 58, Issue 5, 2016, Pages 505-513, ISSN 0033-0620, https://doi.org/10.1016/j.pcad.2015.08.010.
- **Golay, Alain, and Juan Ybarra.** "Link between obesity and type 2 diabetes." *Best practice & research Clinical endocrinology & metabolism* 19.4 (2005): 649-663.
- **Obese, H. J. O. R.** "Body mass index (BMI)." *Obes Res* 6.2 (1998): 51S-209S.
- **Kahn, Barbara B., and Jeffrey S. Flier.** "Obesity and insulin resistance." *The Journal of clinical investigation* 106.4 (2000): 473-481.
- **Rossetti, Lciano, Andrea Giaccari, and Ralph A. DeFronzo.** "Glucose toxicity." *Diabetes care* 13.6 (1990):610-630.

- **Engin, Ayse Basak.** "What is lipotoxicity?." *Obesity and lipotoxicity* (2017): 197-220.
- **de Oliveira Leal, Viviane, and Denise Mafra.** "Adipokines in obesity." *Clinica Chimica Acta* 419 (2013): 87-94.
- **Kim, Jeong-A., Yongzhong Wei, and James R. Sowers.** "Role of mitochondrial dysfunction in insulin resistance." *Circulation research* 102.4 (2008): 401-414.
- **Rajan, S. Sundar, et al.** "Endoplasmic reticulum (ER) stress & diabetes." *Indian Journal of Medical Research* 125.3 (2007): 411-424
- **Cnop, Miriam, Fabienne Foufelle, and Licio A. Velloso.** "Endoplasmic reticulum stress, obesity and diabetes." *Trends in molecular medicine* 18.1 (2012): 59-68
- **Montgomery, Magdalene K., and Nigel Turner.** "Mitochondrial dysfunction and insulin resistance: an update." *Endocrine connections* 4.1 (2015): R1.
- **Vanlint, Simon.** "Vitamin D and obesity." *Nutrients* 5.3 (2013): 949-956.
- **Soskić, Sanja, Edita Stokić, and Esma R. Isenović.** "The relationship between vitamin D and obesity." *Current medical research and opinion* 30.6 (2014): 1197-1199.
- **Pourshahidi, L. Kirsty.** "Vitamin D and obesity: current perspectives and future directions." *Proceedings of the Nutrition Society* 74.2 (2015): 115-124.
- **Pilz, Stefan, et al.** "Role of vitamin D in the development of insulin resistance and type 2 diabetes." *Current diabetes reports* 13 (2013): 261-270.
- **Issa, Claire Michael.** "Vitamin D and type 2 diabetes mellitus." *Ultraviolet Light in Human Health, Diseases and Environment* (2017): 193-205.
- **Rafiq, Shamaila, and Per Bendix Jeppesen.** "Body mass index, vitamin D, and type 2 diabetes: a systematic review and meta-analysis." *Nutrients* 10.9 (2018): 1182.
- **Sung, Chih-Chien, et al.** "Role of vitamin D in insulin resistance." *Journal of biomedicine and biotechnology* 2012 (2012).
- **Talaei, Afsaneh, Mahnaz Mohamadi, and Zahra Adgi.** "The effect of vitamin D on insulin resistance in patients with type 2 diabetes." *Diabetology & metabolic syndrome* 5.1 (2013): 1-5.
- **Zghebi, Salwa S., et al.** "Examining trends in type 2 diabetes incidence, prevalence and mortality in the UK between 2004 and 2014." *Diabetes, Obesity and Metabolism* 19.11 (2017): 1537-1545.
- **Shaw, Jonathan E., Richard A. Sicree, and Paul Z. Zimmet.** "Global estimates of the prevalence of diabetes for 2010 and 2030." *Diabetes research and clinical practice* 87.1 (2010): 4-14.
- **Mohiuddin, A.** "Diabetes fact: Bangladesh perspective." *Community and Public Health Nursing* (2019): 39.
- **Nshisso, Lemba D., et al.** "Prevalence of hypertension and diabetes among Ethiopian adults." *Diabetes & Metabolic Syndrome: Clinical Research & Reviews* 6.1 (2012): 36-41..
- **Lasky, David, et al.** "Obesity and gender differences in the risk of type 2 diabetes mellitus in Uganda." *Nutrition* 18.5 (2002): 417-421.
- **Boutayeb, Abdesslam, et al.** "Estimation of the direct cost of diabetes in the Arabregion." *Mediterranean Journal of Nutrition and Metabolism* 7.1 (2014): 21-32.
- **Sami, Waqas, et al.** "Effect of diet on type 2 diabetes mellitus: A review." *International journal of health sciences* 11.2 (2017): 65.

- **Gupta, Sujaya, et al.** "Status of tobacco smoking and diabetes with periodontal disease." *JNMA: Journal of the Nepal Medical Association* 56.213 (2018): 818.
- **Pavithran, Nivedita, et al.** "South Indian cuisine with low glycemic index ingredients reduces cardiovascular risk factors in subjects with type 2 diabetes." *International journal of environmental research and public health* 17.17 (2020): 6232.
- **Shimazaki, Yoshihiro, et al.** "Relationship between obesity and physical fitness and periodontitis." *Journal of periodontology* 81.8 (2010): 1124-1131.
- **Westerterp, K. R.** "Obesity and physical activity." *International Journal of Obesity* 23.1 (1999): S59-S64.
- **Filali, K. Bertal, N. Oulad Sayad, and A. Diouri.** "P57 Prise en charge de l'HTA chez le diabétique." *Diabetes & Metabolism* 35 (2009): A42.
- **ADVANCE Collaborative Group.** "Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes." *New England journal of medicine* 358.24 (2008): 2560-2572.
- **Tangvarasittichai, Surapon.** "Oxidative stress, insulin resistance, dyslipidemia and type 2 diabetes mellitus." *World journal of diabetes* 6.3 (2015): 456.
- **Westman, Eric C., et al.** "Implementing a low-carbohydrate, ketogenic diet to manage type 2 diabetes mellitus." *Expert review of endocrinology & metabolism* 13.5 (2018): 263-272.
- **Alavudeen, Sirajudeen Shaik, et al.** "Comparative evaluation of biphasic insulin with metformin and triple oral hypoglycemic agents (OHA) in type 2 diabetes patients." *Saudi Pharmaceutical Journal* 28.2 (2020): 210-214.
- **Huang, Mei- Chuan, et al.** "Factors associated with quality of life in patients with diabetic hypoglycaemia." *Journal of Clinical Nursing* 29.9-10 (2020): 1704-1711.
- **Chaudhury, Arun, et al.** "Clinical review of antidiabetic drugs: implications for type 2 diabetes mellitus management." *Frontiers in endocrinology* 8 (2017): 6.
- **Inoue, Hiroyuki, et al.** "Efficacy of DPP-4 inhibitors, GLP-1 analogues, and SGLT2 inhibitors as add-ons to metformin monotherapy in T2DM patients: a model-based meta-analysis." *British journal of clinical pharmacology* 85.2 (2019): 393-402.
- **Sherif, Zaki A., et al.** "Global epidemiology of nonalcoholic fatty liver disease and perspectives on US minority populations." *Digestive diseases and sciences* 61 (2016): 1214-1225.
- **Kashiwagi, Kazuhiro, et al.** "Moderate alcohol consumption is not associated with subclinical cardiovascular damage but with hepatic fibrosis in non-alcoholic fatty liver disease." *Alcohol* 89 (2020): 1-7.
- **Polyzos, Stergios A., Jannis Kountouras, and Christos S. Mantzoros.** "Obesity and nonalcoholic fatty liver disease: From pathophysiology to therapeutics." *Metabolism* 92 (2019): 82-97.
- **Targher, Giovanni, et al.** "Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients." *Diabetes care* 30.5 (2007): 1212-1218.
- **Younossi, Zobair M., et al.** "Nonalcoholic fatty liver disease in patients with type 2 diabetes." *Clinical Gastroenterology and Hepatology* 2.3 (2004): 262-265.
- **Mikolasevic, I., et al.** "Significant liver fibrosis, as assessed by fibroscan, is independently associated with chronic vascular complications of type 2 diabetes: A multicenter study." *Diabetes Research and Clinical Practice* 177 (2021): 108884.
- **Smith, Briohny W., and Leon A. Adams.** "Nonalcoholic fatty liver disease and diabetes mellitus:

pathogenesis and treatment." *Nature Reviews Endocrinology* 7.8 (2011): 456-465.

- **Johnson, Richard J., et *al.*** "Potential role of sugar (fructose) in the epidemic of hypertension, obesity and the metabolic syndrome, diabetes, kidney disease, and cardiovascular disease." *The American journal of clinical nutrition* 86.4 (2007): 899-906.
- **Perdomo, Carolina M., Gema Frühbeck, and Javier Escalada.** "Impact of nutritional changes on nonalcoholic fatty liver disease." *Nutrients* 11.3 (2019): 677.
- **Bocarsly, Miriam E., et *al.*** "High-fructose corn syrup causes characteristics of obesity in rats: increased body weight, body fat and triglyceride levels." *Pharmacology Biochemistry and Behavior* 97.1 (2010): 101-106.
- **Lara-Castro, Cristina, and W. Timothy Garvey.** "Diet, insulin resistance, and obesity: zoning in on data for Atkins dieters living in South Beach." *The Journal of Clinical Endocrinology & Metabolism* 89.9 (2004): 4197-4205.
- **Walker, Celia G., et *al.*** "Diet, obesity and diabetes: a current update." *Clinical science* 112.2 (2007): 93-111.

Webgraphie :

- https://westmedical.com/wp-content/uploads/2022/12/3932e867ae54709fb3d2b4f4ebebca7e6f8f6ff4-1993x1199-1.jpgv
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ANNEXE

People's Democratic Republic of Algeria

Ministry of Higher Education and Scientific Research

MOULAY Tahar University, Saida

Faculty of Sciences

Biology department

Biotechnology vegetal

Questionning : (annexe 01)

1) **Gender :** a) Female ☐ b) Male ☐
2) **Age:** ……...
3) **Lifestyle habits:**
   - a) Cigarette smoke (tobacco) ☐
   - b) Feeding ☐
   - c) Physical activity ☐
4) **Family history of diabetes:**

.....
.....

5) **Year of prevalence of diabetes:** ……..
6) **Weight:..... kg.**
7) **Size.....M.**
8) **Waist circumference:** ……
9) **Body mass index BMI:** ……
10) **Blood glucose:** ……
11) **HbA1c:** ……
12) **The lipid balance:**

……
……
……

J‟ai toujours pensé que la Science est plus grande que les individus qui la font, que l‟insuline parle donc dorénavant d‟elle-même et que son histoire n‟a plus besoin d‟être racontée. » ***F.- G. Banting***

F.-G.Banting