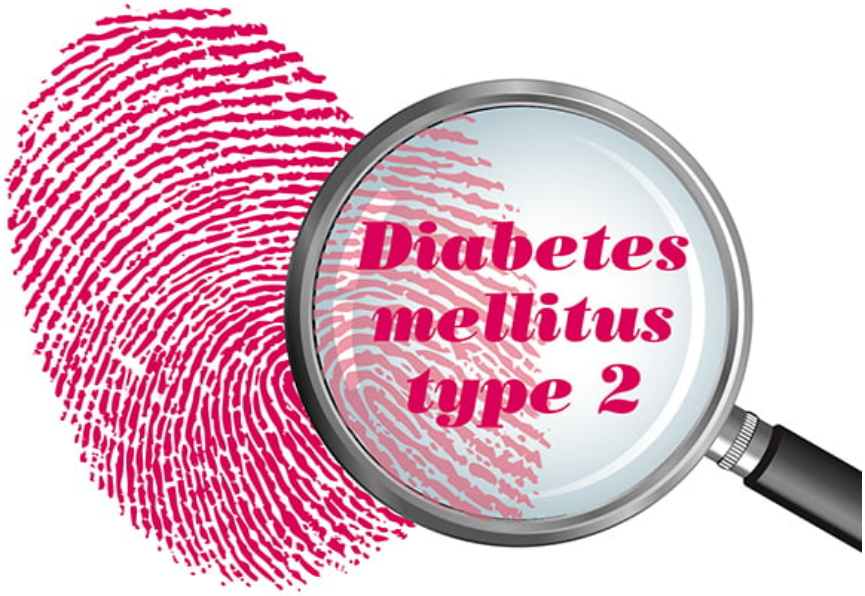
Does osteopathic manipulative treatment have an effect on type 2 Diabetes Mellitus patients?

Literature review



OSTEOPATHIE
College Sutherland

Authors: Omer Ben Zvi and Nino Reus
Promoter: Jeroen de Block
Methodology monitor: Maarten de Boer
Does osteopathic manipulative treatment have an effect on type 2 diabetes mellitus patients?

Graduation assignment nominated with a view to graduate from the Netherlands Academic College for Osteopathy and Mesology (NACOM)

31-08-2022

Table of contents

Abstract

The prevalence of type 2 diabetes mellitus is reaching epidemic proportions. Furthermore, the costs of healthcare due to complications of type 2 diabetes mellitus are rising very fast. Patients with type 2 diabetes mellitus are sometimes treated by osteopaths. They come for other reasons like pain or disability. But are there actually studies that prove that this way of treatment has beneficial effects on patients with diabetes?

Objective
The article's objective is to review the existing evidence on the effect of osteopathic manipulative treatment on type 2 diabetic mellitus patients.

Study design
Literature review

Method
To be able to find the necessary studies a literature search was conducted between May till June 2022 on the following websites:
Google Scholar, PubMed, Cochrane Library, International Journal of Osteopathic Medicine, The Journal of the American Osteopathic Association, Akademie Für Osteopathie, Osteopathic research web and Osteopathic Medical Digital Repository and Science Direct.

Out of the final 24 articles, three were found relevant to this study. Those were assessed with PEDro scale.

Results
Small-scale studies found improvement in patient's parameters after OMT was applied. The findings were as follow: decreased blood glucose level, increased Plasma insulin level, decreased HbA1c value, significantly lowered the severity of low back pain and there is a possible mechanism which reduces circulating levels of TNF-α.

All three articles that were included are low to fair quality RCTs.

Conclusion
Larger and more extensive research needs to be done to be able to evaluate the effectiveness and benefits of OMT on type 2 diabetes mellitus patients, in order to demonstrate clinical significance.
Keywords: diabetes mellitus type 2, osteopathic manipulative treatment

Samenvatting

De prevalentie van diabetes mellitus type 2 wordt hoger en hoger en neigt naar epidemische proporties. Daarnaast stijgen de zorgkosten ook erg snel, onder andere door de complicaties die patiënten met diabetes mellitus type 2 kunnen oplopen. Soms worden patiënten met diabetes mellitus type 2 gezien in de osteopathische praktijk door osteopaten. Maar zijn er eigenlijk onderzoeken die ook daadwerkelijk bevestigen dat osteopathie gunstige effecten heeft voor deze voor deze patiënten?

Doel
Het doel van deze studie is om de literatuur te beoordelen die gaat over de relatie tussen osteopathie en patiënten met diabetes type 2.

Studie
Literatuuronderzoek

Methode
Om de benodigde onderzoeken te verkrijgen, is in de periode van mei tot en met juni 2022 gebruik gemaakt van de volgende websites:
Google Scholar, PubMed, Cochrane Library, International Journal of Osteopathic Medicine, The Journal of the American Osteopathic Association, Akademie Für Osteopathie, Osteopathic research web and Osteopathic Medical Digital Repository and Science direct.

Uiteindelijk waren drie van de 24 gevonden onderzoeken relevant voor deze studie. Deze zijn beoordeeld door middel van de PEDro schaal.

Resultaten
Uit kleinschalige onderzoeken kwam een verbetering van de gebruikte parameters naar voren na een osteopathische behandeling. De bevindingen zijn als volgt: verlaagd bloedglucose, verhoogd insuline level, verlaagde HbA1c waarde, een significante vermindering in lage rugpijn, en een verlaagd serumgehalte van rondcirculerend TNF-α.

Alle drie gebruikte onderzoeken in deze studie betreffen laag tot redelijk kwalitatieve randomised control trials.

Conclusie
Om de effectiviteit en voordelen van een osteopathische behandeling aan te tonen bij patiënten die lijden aan diabetes mellitus type 2, moet groter en meer uitgebreider onderzoek gedaan worden voor een klinische significantie.

Sleutelwoorden: diabetes mellitus type 2, osteopathische behandeling

1. Proem

Writing this thesis marks the end of a four years period of intense study. After learning the osteopathic fundamentals and concepts, it is the right moment to use the acquired knowledge to assist our school with further development in the field of research in osteopathy.

A thesis cannot succeed without the help of others. Therefore, we are very grateful to many people. We would like to express our gratitude in advance to the following persons, who are involved, or indirectly involved, in the realisation of this thesis:

- Omer would like to thank his girlfriend, family and friends for supporting him through all four years.

- Nino would like to thank his parents, family, and friends for all their support, and help in all of his four study years.

- We would like to thank our classmates for sharing their knowledge with us and being available for practice during the study period.

- We are very grateful for all the patients who have come to Amsterdam during our internship every weekend in the last half year of our study.

- Finally, we are very grateful to our two promoters. Jeroen de Block for sharing his knowledge with us, and Maarten de Boer for his methodological assistance.

2. Abbreviations

ADA	American Diabetes Association
AMS	Arteria mesenterica superior
CAD	Coronary artery disease
CEBM	Center for Evidence-Based Medicine
CI	Confidence Interval
CNS	Central nerve system
DM	Diabetes mellitus
DN	Diabetic nephropathy
DPM	Ductus pancreaticus major
DR	Diabetic retinopathy
EBP	Evidence-based practice
FPG	Fasting plasma glucose
GDM	Gestational diabetes mellitus
GIT	Gastrointestinal tract
HbA1c	Haemoglobin A1c
HDL	High-density lipoprotein
IDF	International Diabetes Federation
IL	Interleukins
IR	Insulin resistance
N. X	Nervus Vagus
OGTT	Oral glucose tolerance test
OMT	Osteopathic manipulative treatment
PAD	Peripheral artery disease
PEDro	Physiotherapy Evidence Database
PG	General practitioner
PIR	Pre-absorptive insulin response
QOL	Quality of life
RCT	Randomised controlled trials
RPG	Random plasma glucose
SCFA	Short chain fatty acid
SCOA	Sutherland College for Osteopathy in Amsterdam
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TNF	Tumour necrosis factor
UST	Ultrasound therapy
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor
VMS	Vena mesenterica superior
WHO	World Health Organization

3. Fundamentals

This study forms the first part of a bigger study of Sutherland college for osteopathy in Amsterdam (SCOA) on the effect of osteopathic manipulative treatment (OMT) on type 2 Diabetic Mellitus (T2DM) patients. Because this study is the first part, the fundamentals of T2DM will be reviewed first.

The purpose of this study is to review the available literature on the relationship between OMT and T2DM. The results of this study can be used for further study.

3.1 What is diabetes mellitus and which forms are described?

The term DM is described as a metabolic disorder (World Health Organization, 1999). A Metabolic disorder has been defined by the International Diabetes Federation (IDF). They said "according to the new IDF definition, for a person to be defined as having the metabolic syndrome they must have:

- Central obesity (defined as waist circumference= with ethnicity-specific values)
- Plus, any two of the following four factors:
    - Raised triglycerides or specific treatment for this lipid abnormality;
    - Reduced high-density lipoprotein (HDL) cholesterol or specific treatment for this lipid abnormality;
    - Raised blood pressure or treatment of previously diagnosed hypertension;
    - Raised fasting plasma glucose or previously diagnosed T2DM" (International Diabetes Federation, 2006).

DM is probably one of the oldest known diseases in humanity (Baynes, 2015). 3000 years ago, back in 1500 B.C., it was reported by the ancient Egyptians for the first time (Ahmed, 2002; Lakhtakia, 2013). The word diabetes means "siphon" in Egypt. The definition of this word is frequent urination, a major symptom of DM (Science Encyclopedia, 2022).

In 1776, Dobson, a British man, firstly confirmed the presence of an increased value of sugar in urine and blood. In 1889, researchers discovered that in the pathogenesis of diabetes mellitus (DM), the pancreas plays a role. They found that removal of the pancreas leads to diabetes (Ahmed, 2002; Cecil, 1908; Lakhtakia, 2013). So, this means that the function of the pancreas plays a major role in the origin of DM.

The distinction between type 1 DM (T1DM) and T2DM was made in 1936. In 1986, T2DM was first described as one of the components of a metabolic syndrome (Baynes, 2015).

Moreover, in the Journal of Diabetes and Metabolism, Baynes J. defined DM as "a metabolic disorder characterized by the presence of chronic hyperglycaemia either immune-mediated (Type 1 DM), insulin resistance (IR) (Type 2), gestational or others (environment, genetic defects, infections, and certain drugs)" (2015).

3.1.1 Classification of diabetes mellitus

Several types of DM exist, namely T1DM, T2DM, and gestational diabetes mellitus (GDM). T1DM is caused by an autoimmune process, which leads to insulin-producing bèta-cell destruction (Ozougwu, 2013). Meanwhile, GDM, a temporary type of DM, is an operational classification that is first detected during pregnancy (Baynes, 2015). According to the American Diabetes Association, the definition of GDM is "a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both" (American Diabetes Association, 2009).

Because of the relevance of this study, a closer look is taken at T2DM in the next paragraph.

3.1.1.1 Type 2 diabetes mellitus.

T2DM, or non-insulin-dependent diabetes mellitus, has the biggest prevalence in our society nowadays. T2DM has become one of the biggest public health challenges around the world today. People's lifestyles have changed fast in this last century, especially their dietary habits. The increasing intake of fat, salt, and sugar, leads to more and more people with metabolic syndrome (Ma et al., 2019). Some other possible explanations for this rapidly increasing rate are an increasing incidence of obesity, reduced physical activity levels as countries become more industrialized, and ageing of the population (Gurung et al., 2020).

According to Chatterjee et al. (2017), more than 90% of patients with diabetes suffer from T2DM. Other researchers suggest it is around 80%. Data suggest that about 1 out of 4 persons with DM are unaware of their disease in the USA (Vijan et al., 2010).

T2DM may present with some characteristic symptoms, like thirst, polyuria, blurring of vision, and weight loss. In the long term, the effects of T2DM may be dysfunction and failure of various organs (World Health Organization, 1999).

Nowadays, more than 400 million people suffer from T2DM worldwide. The incidence is expected to continue to rise (Javeed & Matveyenko, 2018; Khursheed et al., 2019). These incredibly high numbers suggest there is an urgent need for preventive and treatment strategies.

3.2 What are the causes of type 2 diabetes mellitus type?

The absolute cause of T2DM is still unknown today. T2DM seems to be the result of an interaction between genetic and environmental factors. However, the mode of inheritance and the factors are not known for this type of DM.

3.2.1 Genetic

The genetic association plays a major role in T2DM, more than in T1DM (Homsi & Lukic, 1993). In Finland, a twin study has shown a concordance rate for T2DM of a maximum of 40% (Kaprio et al., 1992). Some other studies have reported much higher rates. S. Rich reported a monozygotic twin rate of T2DM of almost 100% in 1990 (Rich, 1990). However, Newman et al reported a rate of 58% (Newman et al., 1987). The research of Kaprio et al. has been done on a population of 505 individuals with T2DM monozygotic or dizygotic. Meanwhile, the research of Newman et al. has been done on a population of people with a minimum age of 50 years who were all in the army. The research of S. Rich does not show the composition of the research group. Therefore, this study is difficult to be assessed by someone else.

Research has shown that the prevalence of T2DM in ethnic groups in some developing countries is high (Homsi & Lukic, 1993). This can indicate that genetic factors are more important than environmental factors.

3.2.2 Lifestyle

In some lifestyle-modification studies, a demonstration of T2DM remission highlights the predominant role of acquired alterations (Gujral et al., 2013; Roden & Shulman, 2019). A study by Kolb and Martin has even shown that the duration and quality of sleep are contributing factors to the pathogenesis of T2DM (Kolb & Martin, 2017).

3.2.3 Pancreas and insulin role

T2DM is characterised by deficient insulin secretion by pancreatic islet bèta-cells in the context of impaired insulin sensitivity, which is termed insulin resistance (IR). Insulin sensitivity is mostly dependent on the following three factors:

- Age;
- Sex;
- Weight gains.

The sensitivity of insulin declines decades before T2DM onset, which represents one of the earliest pathogenic events of T2DM. Initially, bèta-cells are going to compensate for an IR by secreting more insulin. This results in hyperinsulinaemia, which can lead to hepatic de novo lipogenesis, steatosis, and hyperlipidaemia. An increased glycerol flux to the hepar stimulates gluconeogenesis. Combined with a decline of the bèta-cell function, this leads to fasting and postprandial hyperglycaemia. Without losing weight, IR and bèta-cell dysfunction occur simultaneously and continuously, which leads to an increased risk of comorbidities (Kahn, 2003; Roden & Shulman, 2019).

3.3 Anatomy and physiology of the pancreas

To understand the pathophysiology of T2DM, there must be some knowledge of embryology, anatomy, and physiology of the pancreas. Furthermore, to understand what are the relationships of the pancreas with its environment.

3.3.1 Embryology in short

From an embryologic point of view, the pancreas has developed from the endodermal lining on the border between the primitive foregut and midgut in two separate parts. These two buds arise as diverticula of the caudal end of the primitive foregut during the fourth week of development. The dorsal pancreatic bud lies in the dorsal mesentery, and the ventral pancreatic bud is close to the ductus choledochus. When the duodenum rotates clockwise, the ventral pancreatic bud moves to the dorsal and comes to lie immediately below and behind the dorsal bud (de Block, 2022; Gittes, 2009; Pan & Wright, 2011; Sadler, T.W., 2015).

Out of these two buds, two drains have been created, the ductus pancreaticus (ductus pancreaticus of Wirsung, or ductus pancreaticus major (DPM)) and ductus accessorius (ductus accessories of Santorini or ductus pancreaticus minor). There are many variations in the location of these drains due to the embryological rotation. An important embryonal connection can be found in the relationship between the pancreas and vesica biliaris by the ductus choledochus (Bockman, 1993; ‘Ductus pancreaticus’, 2020; ‘Ductus pancreaticus accessorius’, 2014; Mahadevan, 2019).

The portion of the dorsal mesogastrium fuses with the dorsal body wall. This causes the tail of the pancreas to lie against the dorsal body wall. Due to some rotations of the gaster, and the position of the spleen, the cauda of the pancreas comes to lie between the two leaves of the dorsal mesogastrium. Later, with some

further development, the pancreas assumes a secondarily retroperitoneal position, which is shown in figure 1 (Muts, 2010; Sadler, T.W., 2015).

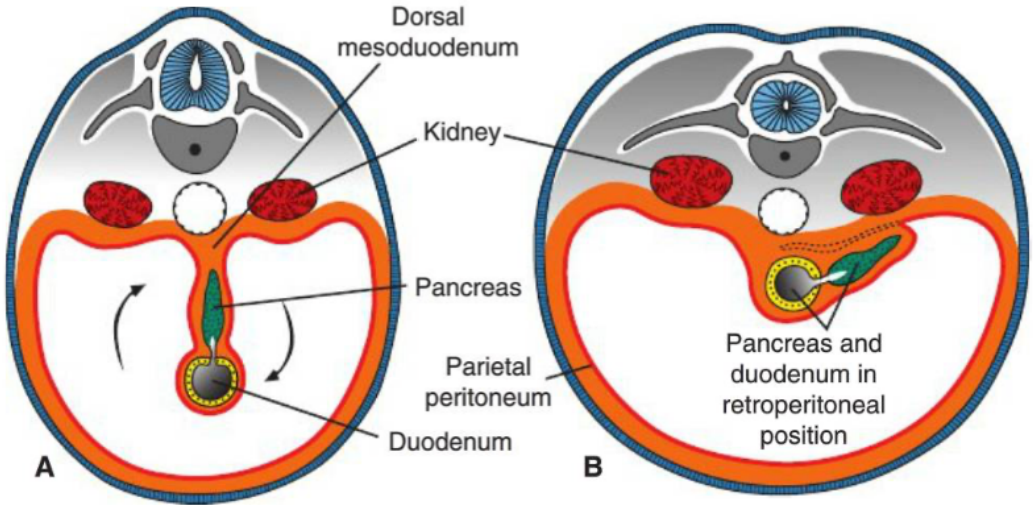


Figure 1

Transverse Sections through the Region of Duodenum and Pancreas at Various Stages of Fetal Development.

Note 1. (A) First, Duodenum and Caput Pancreaticus are located in the Median Plane. (B) Later, Duodenum and Pancreas Rotate to the Right and Acquire a Retroperitoneal Position.
Note 2. Received from Sadler, T.W. (2015). Langman's Medical Embryology (thirteenth). Wolters Kluwer Health.

In the third fetal month, the pancreatic Islets of Langerhans develop from the parenchymatous pancreatic tissue, just like the glucagon- and somatostatin-secreting cells. Then, the Islets of Langerhans spread over the whole pancreas. The visceral mesoderm forms the pancreatic connective tissue and surrounds the pancreatic bud (Sadler, T.W., 2015).

3.3.2 Anatomy

The pancreas is part of the gastrointestinal tract (GIT) and is located secondary retroperitoneal at the level of L1-L3 on the posterior wall of the abdominal cavity. This digestive gland can be divided into five parts, which are the caput, collum, corpus, cauda, and processus uncinatus (Henry et al., 2018; Mahadevan, 2019).

The head of the pancreas, caput pancreaticus, is surrounded by the duodenum on the right side. The processus uncinatus is tucked behind the vasa mesenterica superior. It lies anterior to the aorta and posterior to the arteria mesenterica superior (AMS) (Bockman, 1993; Kiegerl, 2006). On the left side, the cauda pancreaticus extends to the hilus of the left kidney and is touching the spleen

anteriorly. These relationships can be seen in figure 2 (The Pancreas in Situ (Netter, F.H., Atlas of Human Anatomy. 6th Ed. 2014, Saunders), 2021).

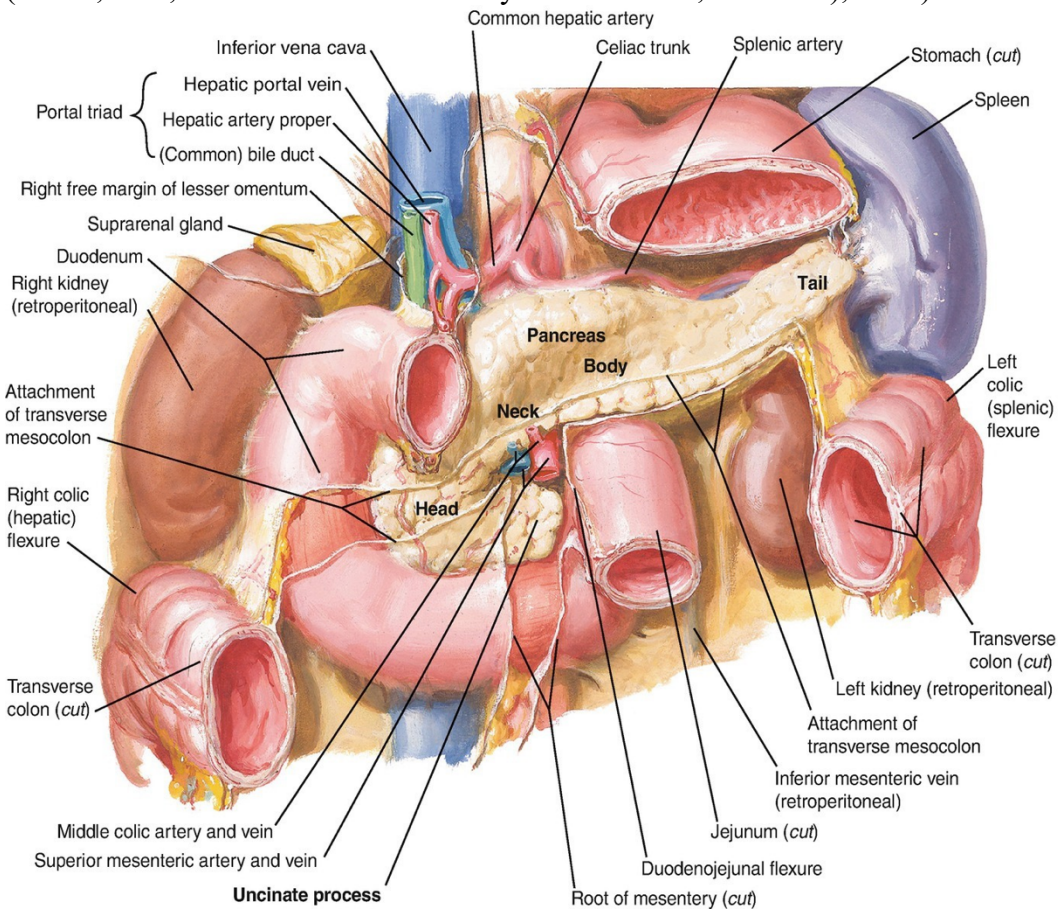


Figure 2

The Pancreas and his Environment.

Note. Received from Netter, F. H. (2006). Atlas of Human Anatomy.

The posterior surface of the pancreas is related to the left and right kidneys, glandulae suprarenales, arteriae and venae renales, aorta, and vena cava inferior. These relationships are without any intervention of the peritoneum (Bockman, 1993; Muts, 2010).

3.3.2.1 Blood supply

Due to the embryologic development of the pancreas, the vasculature of this organ is strongly associated with the vasculature of the primitive foregut and primitive midgut. Like the whole tractus digestivus, the arterial supply of the pancreas is marked by numerous anastomoses. In 1742, the double arterial arcades anterior and posterior to the head of the pancreas is first recognized. These arcades are serving both the duodenum and pancreas (Woodburse & Olsen, 1951). The caput pancreaticus and duodenum are supplied with a double arterial circle. These two

organs are supplied by branches of the truncus coeliacus and the AMS. Three major branches are given off from the truncus coeliacus. These are the arteria gastrica sinistra, arteria lienalis, and arteria hepatica propria. The pancreas is richly supplied by branches from the arteria hepatica propria and lienalis (Bockman, 1993; Henry et al., 2018). An overview of the arterial supply of the pancreas is given in figure 3 (Mahadevan, 2019).

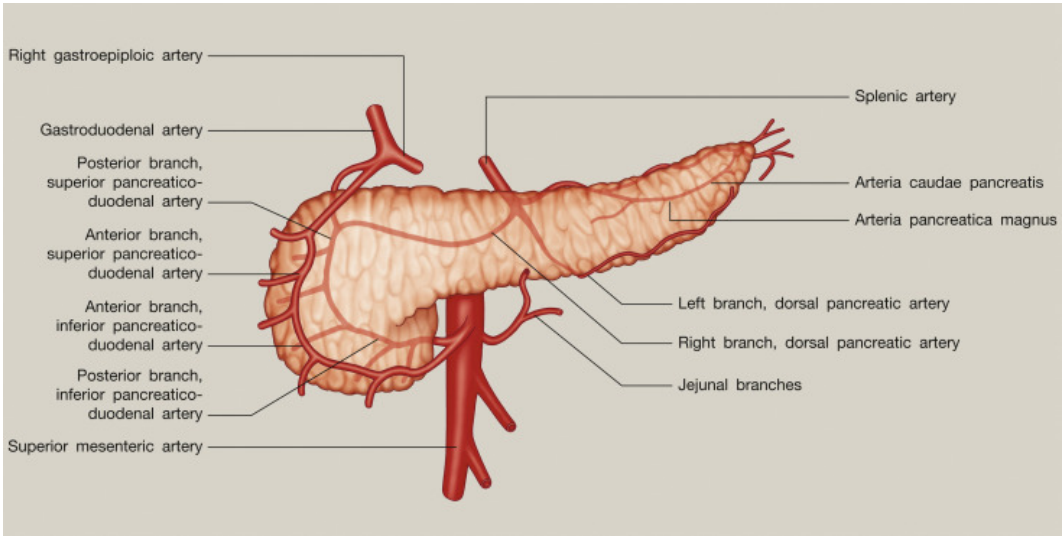


Figure 3

Arterial Supply of Pancreas.

Note. Received from Mahadevan, V. (2019). Anatomy of the pancreas and spleen. Surgery (Oxford), 37(6), 297–301. https://doi.org/10.1016/j.mpsur.2019.04.008

The venous drainage is provided by the vena portae. This vein originates from three different vessels, the vena mesenterica superior (VMS) and inferior, and the vena lienalis. I n brief, the veins of the pancreas drain to the VMS, vena lienalis, and vena cavae (Henry et al., 2018).

In parallel with the AMS, the VMS passes the processus uncinatus anteriorly. The vena portae passes through the omentum minus to the porta hepatis. The vena pancreaticoduodenale drains into the VMS and vena portae. The pattern for anastomosis and drainage of the venous system is much more irregular than the pattern of the arterial system (Bockman, 1993). An overview of the venous drainage can be seen in figure 4 (Mahadevan, 2019).

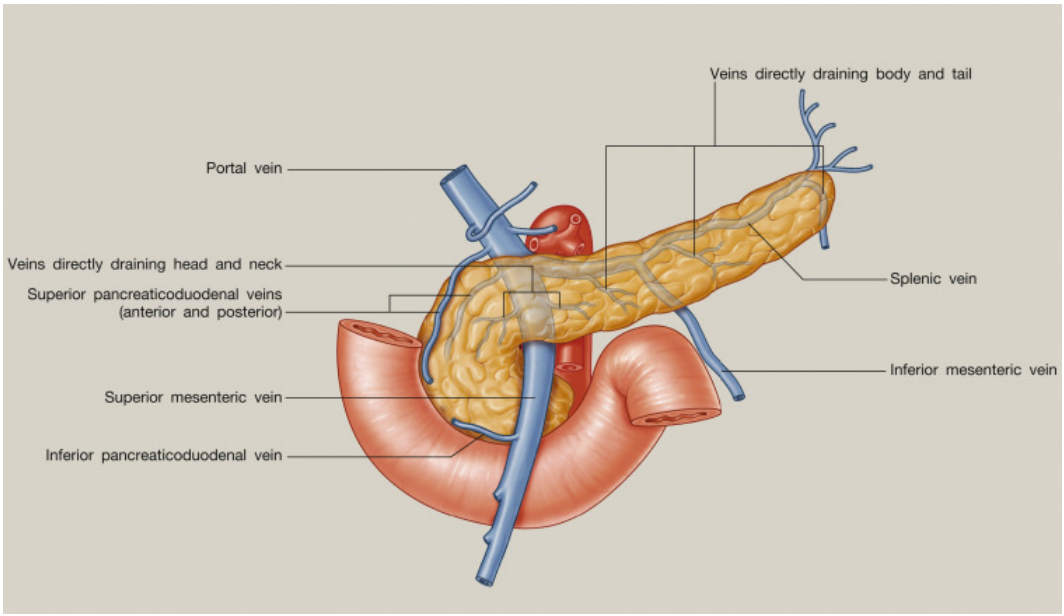


Figure 4

Venous Drainage of the Pancreas.

Note. Received from Mahadevan, V. (2019). Anatomy of the pancreas and spleen. Surgery (Oxford), 37(6), 297–301. https://doi.org/10.1016/j.mpsur.2019.04.008

3.3.2.2 Lymphatic system

Within the pancreas, a network of lymphatic vessels exists. Under physiologic conditions, the lymphatics are not particularly prominent (Bockman, 1993). In some random areas, both intra- and interlobular lymphatics come into a close relationship with acinar cells. However, research has shown that there is certainly no close or consistent affinity with the Islets of Langerhans. Affinity with the Islets of Langerhans is only where lymphatic vessels in connective tissue septa pass close to a pancreatic lobule that contains an islet at its periphery (O'Morchoe, 1997).

3.3.2.3 Innervation

The innervation of the tractus digestivus can be subdivided into intrinsic and extrinsic components. The intrinsic component consists of neuronal cell bodies and nerve processes of the enteric neurons. And the extrinsic component consists of nerve fibres and cellular bodies localized outside the GIT. This part belongs to the sympathetic and parasympathetic systems (Hansen, 2003; Salvioli et al., 2002).

The parasympathicus is identified by the Nervus Vagus (N. X) anterior and posterior. This nerve reaches the pancreas directly or passes across the preaortic chain of the sympathetic ganglia. The parasympathetic system provides a part of

the secretory stimulus for the pancreas (Bockman, 1993; Hansen, 2003; Salvioli et al., 2002).

On the other hand, the sympathicus is identified by the nervus splanchnicus. The neural cell bodies of these neurons are located in the ganglia coeliacus, and mesenterica superior. The function of the afferent part of this system is primarily sensory or pain transmission to the central nervous system (CNS). This system is composed of thin unmyelinated fibres running with either the parasympathetic pathways or the sympathetic inputs (Salvioli et al., 2002). The schema of pancreatic innervation is shown in figure 5 (Netter, 2006).

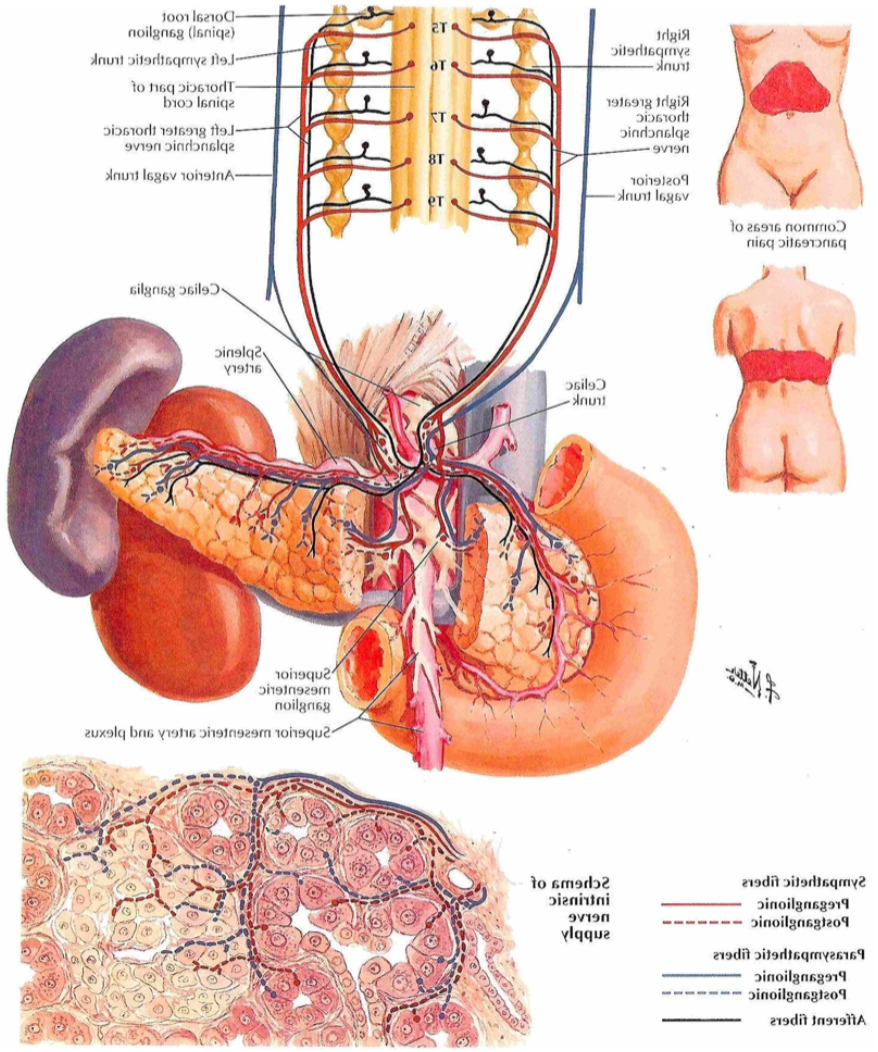


Figure 5

Schema of Pancreatic Innervation.

Note. Received from Netter, F. H. (2006). Atlas of Human Anatomy.

3.3.3 Histology

After enquiring the knowledge over the anatomical structures of the pancreas, the histology of the panaceas can be explained. T2DM diabetes does not occur without progressive bèta-cell dysfunction (Nugent et al., 2008). These cells are located in the Islets of Langerhans. From a histological point of view, it is important to know what these consist of for understanding the full context of T2DM.

3.3.3.1 Islet of Langerhans

In 1869 P. Langerhans first described groups of cells that are situated between the acini and differ markedly from those of the ordinary glandular type. These groups are designated the "Islands of Langerhans" (Opie, 1901). The Islets of Langerhans collectively comprise the endocrine pancreas that synthesizes and secretes insulin, glucagon, PP, and somatostatin (Mahadevan, 2019). Small Islets are dispersed throughout the acinar lobules. The larger Islets lie along the DPM and interlobular ducts of the pancreas (Beger et al., 2018).

The majority of islet cells are bèta-cells (75–80%), followed by alpha-cells (about 15%), δ-cells (about 5%), and very few PP-cells. In the processus uncinatus, Islets contain few alpha-cells and many more PP-cells (Beger et al., 2018). According to Stefan et al. (1982), PP-cells are the second most prevalent endocrine cell type of the pancreas.

In their article, Weir and Bonner-wier (1990) stated that “Islet secretion is drastically altered in virtually all forms of diabetes”. Moreover, they say that the most evident change is the one of bèta-cell deficiency which leads to reduced insulin secretion.

3.3.4 Physiology

From physiologically perspective the pancreas is the most important digestive gland. The functions of the pancreas can be subdivided into two groups, an endocrine and an exocrine part. The exocrine part of the pancreas is the part that produces and secretes digestive enzymes into the duodenum and includes acinar cells (Pan & Wright, 2011; Reichert & Rustgi, 2011). On the other hand, the endocrine part of the pancreas produces and secretes hormones into the blood to regulate energy metabolism and storage (Longnecker, 2014).

3.3.4.1 Endocrine organ

The endocrine part of the pancreas consists of five different types of cells (Pan & Wright, 2011). All of these cells secrete a different type of hormone. The name of these cells and their secretion products are described in table 1.

Table 1
An *O*verview of the *D*ifferent *T*ypes of *C*ells of the *E*ndocrine *P*ancreas.

Cell	Secretion product
Alpha-cells	Glucagon
Bèta-cells	Insulin
Delta-cells	Somatostatin
PP-cells / gamma-cells	Polypeptide
Epsilon cells	Ghrelin

Glucagon and insulin are the most important type of hormones related to T2DM secreted by the endocrine pancreas, because of their function in the glucose metabolism. Therefore, both hormones are briefly described below.

3.3.4.1.1 Insulin

Insulin is secreted by the pancreatic bèta-cells. It promotes carbon energy deposition in the body, and its main function is the regulation of whole-body glucose homeostasis and peripheral tissue glucose uptake (Watson & Pessin, 2001). The blood level of insulin is regulated in different organs, but it starts all with the production in the bèta-cells of the pancreas. Insulin affects many different cells, such as cells in the brain, muscle fibres, and adipocytes. The journey of insulin is shown in figure 6 (Tokarz et al., 2018).

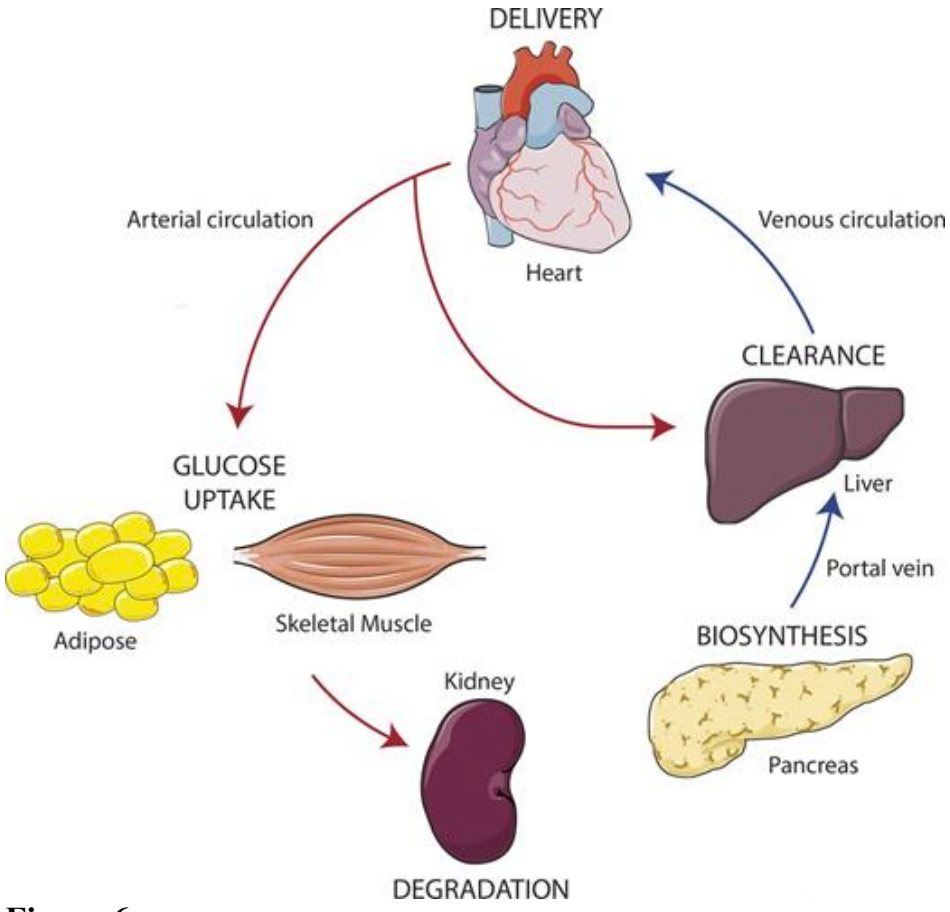


Figure 6

Journey of Insulin in the Body.

Note. Received from Tokarz, V. L., MacDonald, P. E., & Klip, A. (2018). The cell biology of systemic insulin function. Journal of Cell Biology, 217(7), 2273–2289. https://doi.org/10.1083/jcb.201802095

3.3.4.1.2 Glucagon

Another important hormone of glucose metabolism is glucagon. This hormone is secreted by the alpha-cells and has the opposite effect of insulin.

As well as the bèta-cells of the pancreas, regulation of the alpha-cell function is complex. Nutrients, neurologic, and hormonal influences exist on glucagon secretion. The most important physiological regulator of the alpha-cells is glucose, which suppresses the secretion of glucagon (Dunning et al., 2005).

According to Li and Zhuo (2013), there is evidence that hyperglucagonaemia (excessive glagon in the blood) plays a role in the development of T2DM. As with bèta-cell dysfunction in T2DM, most of the abnormalities of alpha-cell function may be considered to reflect an impairment of glucose sensing. A fasting hyperglucagonaemia contributes to the increased rate of hepatic glucose output, which is seen in patients with T2DM. However, according to Li and Zhuo (2013),

it is very difficult to demonstrate a direct relationship between hyperglucagonemia and T2DM.

3.3.4.1.3 Regulation of the endocrine pancreas.

The endocrine system of the pancreas is the one of more importance by diabetic patients. Circulating glucose controls the secretion of hormones from the Islets of Langerhans. These hormones must be supplied to the body tissues in amounts and time dynamics that maintain plasma glucose within a very narrow concentration range (Ferrannini & Mari, 2004). Glucose stimulates insulin secretion and inhibits glucagon secretion. Furthermore, the endocrine pancreas derives additional information about the incoming nutrients. Numerous gastrointestinal hormones, which are released by different parts of the intestines, give information to the Islet of Langerhans. Several of these hormones are capable to influence the secretion of glucagon and insulin, which fulfils metabolic needs (Strubbe & Steffens, 1993).

Additionally, over the last several decades, there is increasing evidence for the participation of the CNS in blood glucose homeostasis via a direct innervation of the hepar and the pancreas (Marty et al., 2007).

Glycaemic homeostasis depends on three processes that take place simultaneously and which must be coordinated by: (Lippi et al., 1994)

- Insulin secretion;
- Stimulation of glucose uptake;
- The suppression of the hepatic production of glucose.

Kaneto et al. (1967) showed in their study that a stimulation of the dorsal vagal trunk results immediately in increasing insulin secretion. This suggests that N. X plays an important role in the causation of the pre absorptive Insulin Response (PIR). The absence of this mechanism could be responsible for wider fluctuations in blood glucose. (Strubbe & Steffens, 1993).

Furthermore, there are some (neuro)peptides and hormones that affect the pancreas. An overview is given in table 2 (Chandra & Liddle, 2009; Morioka et al., 2007).

Table 2
An Overview of (Neuro)peptides and Hormones Affecting the Endocrine Pancreas.

Product	Function
Orexin A and B	Decrease the secretion of glucagon
Arginine vasopressin, corticotropin releasing hormone, and adrenocorticotropic hormone.	Stimulate secretion of cortisol
Neuropeptide Y	Inhibit the secretion of insulin
Glucagon-like peptide-1	Stimulate secretion of insulin and somatostatin Inhibit secretion of glucagon
Leptin	A homeostatic role in the function of the endocrine pancreas under normal, as well as under stressful conditions

Leptin, a peptide hormone, acts as a satiety hormone and is related to T2DM ('Leptine', 2020). Leptin, secreted by white adipose tissue, inhibits the feeling of hunger (Mantzoros, 1999). When this process is not working well, an increased risk of developing obesity will appear. Obesity, hypertension, and IR are closely related in humans. However, although IR has been associated with increased leptin levels in one study in humans (Segal et al., 1996), according to C.S. Mantzoros, several independent studies have shown that serum leptin levels are similar in patients with T2DM and control groups (Mantzoros, 1999).

3.3.4.2 Exocrine organ

In addition to its endocrine functions, the pancreas also functions as an exocrine organ. The acinar cells synthesize and secrete digestive enzymes which contribute to the digestion of food.

3.4 Pathogenesis of type 2 diabetes mellitus

Olokoba et al. (2012) said in their study: "T2DM is characterized by insulin insensitivity as a result of IR, declining insulin production, and eventually pancreatic beta-cell failure. This leads to a decrease in glucose transport into the liver, muscle cells, and fat cells. There is an increase in the breakdown of fat with hyperglycemia". Figure 7 shows in simple this process (Ozougwu, 2013). Recently, the involvement of impairment of the function of alpha-cells has been recognized in the pathophysiology of T2DM (Olokoba et al., 2012).

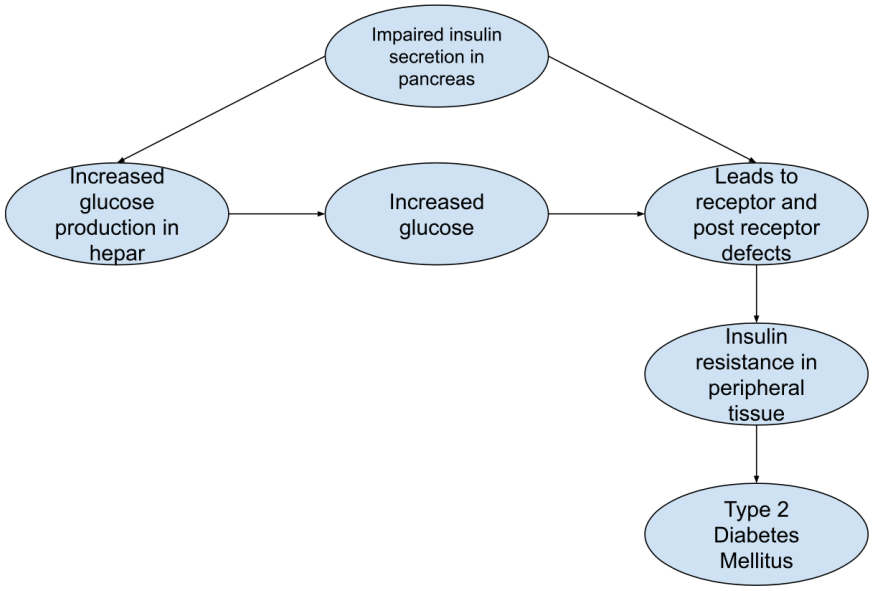


Figure 7

Pathogenesis of Type 2 Diabetes Mellitus.

Note. Received from Ozougwu, O. (2013). The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus. Journal of Physiology and Pathophysiology, 4(4), 46–57. https://doi.org/10.5897/jpap2013.0001

Dysfunction of the pancreatic alpha-cells causes rising glucagon levels during fasting. These levels will not be suppressed by a meal, which results in hyperglycaemia due to inadequate levels of insulin and increased IR (Fujioka, 2007; Olokoba et al., 2012).

Patients presenting with T2DM show a more gradual loss of insulin signaling through multifactorial mechanisms including IR and β-cell dysfunction. IR is characterized by desensitization to insulin-dependent processes, including glucose uptake in insulin-sensitive tissue, glycogenesis, suppression of adipose tissue lipogenesis and hepatic glucose output (Nugent et al., 2008).

The biggest part of people suffering from T2DM is obese, with central visceral adiposity. This adipose tissue plays a crucial role in the pathogenesis of T2MD. The predominant theory which is used to explain this connection is the portal/visceral hypothesis (Olokoba et al., 2012; Ravussin & Smith, 2002). According to Ravussin and Smith, three statements support this theory:

1. “Lipodystrophy, a failure to develop adequate adipose tissue mass. This results in severe IR and DM. This is thought to be the result of ectopic storage of lipids into the liver, skeletal muscle, and the pancreatic insulin-secreting bèta-cell.

2. Most obese patients also shunt lipid into the skeletal muscle, the liver, and probably the bèta-cell. The degree of lipid infiltration into skeletal muscle and liver correlates highly with IR.
3. Increased fat cell size. This is highly associated with IR and the development of DM. The increased size of a fat cell may represent the failure of the adipose tissue mass to expand. And to accommodate an increased energy influx." (Ravussin & Smith, 2002).

As described above, obesity has a strong effect on the development of T2DM. Homsi and Lukic said in their study about the relationship between obesity and T2DM: "It is more than just a risk factor for T2DM, it has a causal effect on the development of T2DM against a genetic background. The evolution from obesity to T2DM results from a succession of four pathophysiological events:

1. Augmentation of the adipose tissue mass, leading to an increased lipid oxidation.
2. IR is noted early in obesity, which blocks the function of the glycogen cycle.
3. Despite maintained insulin secretion, unused glycogen prevents further glucose storage leading to T2DM.
4. Complete bèta-cell exhaustion appears later" (Homsi & Lukic, 1993).

According to a study of Schmidt et al. patients with a central type of obesity show a higher rate of IR, T2DM, hyperlipidaemia, hypertension and premature mortality (Schmidt et al., 1992).

In addition to an increased caloric intake and decreased energy expenditure, other environmental factors appear important too (Kahn et al., 2014). In 2001, a study by Hu et al. indicates that increased amounts of trans and saturated fat are important in determining the development of obesity, IR, and bèta-cell dysfunction. They said, "Dietary recommendations to prevent T2DM should focus more on the quality of fat and carbohydrate in the diet than quantity alone, in addition to balancing total energy intake with expenditure to avoid overweight and obesity" (Hu, van Dam, et al., 2001).

Further, ageing may play a role in declining glucose tolerance by an ageing-associated reduction in the bèta-cell's responsiveness to carbohydrates (Chen et al., 1988). Whereas, the article of Guénard et al. stated that the risk of developing obesity and T2DM may be already in the in-utero environment determined, part by the mother's habits (Guénard et al., 2013).

From a different angle, a major key regulator of the pancreatic metabolic process is the nervous system. Both sympathetic and parasympathetic nervous systems control glucose metabolism directly through neuronal input and indirectly via circulation to influence the secretion of insulin and glucagon and the production

of hepatic glucose (Nonogaki, 2000; Porte, 1969). In humans, N.X is important in regulating the islets as severing this nerve results in impaired insulin secretion (Miller, 1981). In 1979, a study by Berthoud and Jeanrenaud showed that ablation of the hypothalamus in rats results in dysregulation of the bèta-cells and the development of hyperinsulinaemia (Berthoud & Jeanrenaud, 1979). This brain region also regulates hepatic glucose production via the action of insulin, glucose and fatty acids (Obici et al., 2002).

3.4.1 Role of gut microbiota in Type 2 diabetes mellitus

Another cause of T2DM can be the gut microbiota. The GIT is the primary site of interaction between the host immune system and microorganisms. These microorganisms can be symbiotic or pathogenic, and act as a protective mediator during pathological conditions (Zhang & He, 2015). Microbiota is composed of microorganisms that not only monitor the body's homeostasis, but are also the driving force in the pathogenesis of the metabolic disease. These microbiotas are influenced by changes in diet and by disease, which causes a variety of new strains (Prakash et al., 2011; Tilg & Kaser, 2011; Woldeamlak & Biadgo, 2019).

An important duty of intestinal bacteria is to generate short-chain fatty acids (SCFAs) by fermenting dietary carbohydrates. The function of these SCFAs is to enhance the gut wall integrity and prevent metabolic endotoxemia, and inflammation.

Nowadays, there is increasing evidence of changes in the gut microbiota composition or function in T2DM patients. These bacteria of dysbiosis in patients with T2DM are involved predominantly in the control of inflammation and energy homeostasis. Those alterations in the microbiome fermentation profile change the gut permeability and energy homeostasis. Due to the changed gut permeability, an extraintestinal infiltration of lipopolysaccharides causes endotoxemia, which results in low-grade inflammation. The inflammation is triggered by endotoxins in the extraintestinal tissue. Poor energy homeostasis leads to hyperglycaemia and hyperlipidaemia, which may lead to obesity and ultimately bèta-cell destruction or IR (Sohail et al., 2017; Woldeamlak & Biadgo, 2019).

3.5 Complications of type 2 diabetes mellitus

Patients diagnosed with T2DM are having increased risk to many complications. These are mainly due to complex and interconnected mechanisms, such as hyperglycaemia, IR, low-grade inflammation and accelerated atherogenesis (Schlienger, 2013). Managing all of these complications brings substantial financial costs to health care (Johnson & Shubrook, 2013).

In some cases, patients get a severe form of T2DM, which can lead to ketoacidosis or a non-ketonic hyperosmolar state. Eventually, it may lead to stupor, coma, and, in absence of effective treatment, death. However, the symptoms are not this severe in most cases. And sometimes even absent. Consequently, hyperglycaemia sufficient to cause pathological and functional changes may be present for a long time before the diagnosis is made (Engerman, 1989). The complications of T2DM can be subdivided into two groups, which are described in Table 3 (Woldeamlak & Biadgo, 2019).

Table 3

The Harmful Effects of Hyperglycaemia can be Separated into Microvascular Complications and Macrovascular Complications.

Microvascular complications	Macrovascular complications
Diabetic retinopathy	Coronary artery disease
Diabetic nephropathy	Peripheral arterial disease
Diabetic neuropathy	Stroke

Note. Received from Woldeamlak, B., & Biadgo, K. Y. and B. (2019). Role of Gut Microbiota in Type 2 Diabetes Mellitus and Its Complications: Novel Insights and Potential Intervention Strategies. The Korean Journal of Gastroenterology, 74(6), 314–320. https://doi.org/10.4166/kjg.2019.74.6.314

Despite not being directly related to this study, these complications will be briefly viewed. Because these can all occur in the osteopathic practice. Osteopaths must know what the complications of T2DM are and recognize these, so that they are warned against possible (relative) red flags.

3.5.1 Diabetic retinopathy

One of the most common complications of T2DM is diabetic retinopathy (DR). Furthermore, DR is the leading global cause of vision loss in working middle-aged adults. This pathology involves anatomic changes in retinal vessels and neuroglia (Falcão et al., 2022; Wang & Lo, 2018).

3.5.2 Diabetic nephropathy

Diabetic nephropathy (DN) is the leading cause of end-stage renal disease worldwide and is one of the most frequent and severe complications of DM (Vikram et al., 2019). The main high-risk factors for the development of DN are chronic hyperglycaemia and hypertension.

3.5.3 Diabetic neuropathy

Diabetic neuropathy is another very common complication of T2DM. The most common form of this complication is distal symmetric polyneuropathy (Bansal et al., 2006). The hands and lower limbs are commonly affected by distal symmetric polyneuropathy (Feldman et al., 2019).

3.5.4 Coronary artery disease

According to a study by Aronson and Edelman in 2014, coronary artery disease (CAD) is a major determinant of the long-term prognosis among patients with DM (Aronson & Edelman, 2014). CAD is a major contributor to mortality and morbidity among T2DM (Al-Nozha et al., 2016; Arvind et al., 2002). This complication is a red flag for manipulations.

3.5.5 Peripheral artery disease

Another complication of T2DM can be Peripheral artery disease (PAD). This is an arterial condition, which is characterized by atherosclerotic occlusive disease of the lower extremities. This complication is a red flag for manipulations too.

3.5.6 Stroke

The last possible complication of T2DM, which will be reviewed in this study, is stroke. Patients with DM are at increased risk of hypertension and represent a strong independent risk factor of stroke, mainly for ischemic stroke (R. Chen et al., 2016; Mankovsky & Ziegler, 2004).

DM can cause pathologic changes in blood vessels at various locations. These possible changes include vascular endothelial dysfunction, increased early-age arterial stiffness, systemic inflammation and thickening of the capillary basal membrane. Besides, abnormalities in the early left ventricular diastolic filling are commonly seen in T2DM. The possible mechanisms of congestive heart failure in T2DM can be seen in figure 8 (R. Chen et al., 2016). This figure is also shown that arterial diseases are a common complication of T2DM. So, an osteopath must be aware of this at any time related to the possible (relative) red flags.

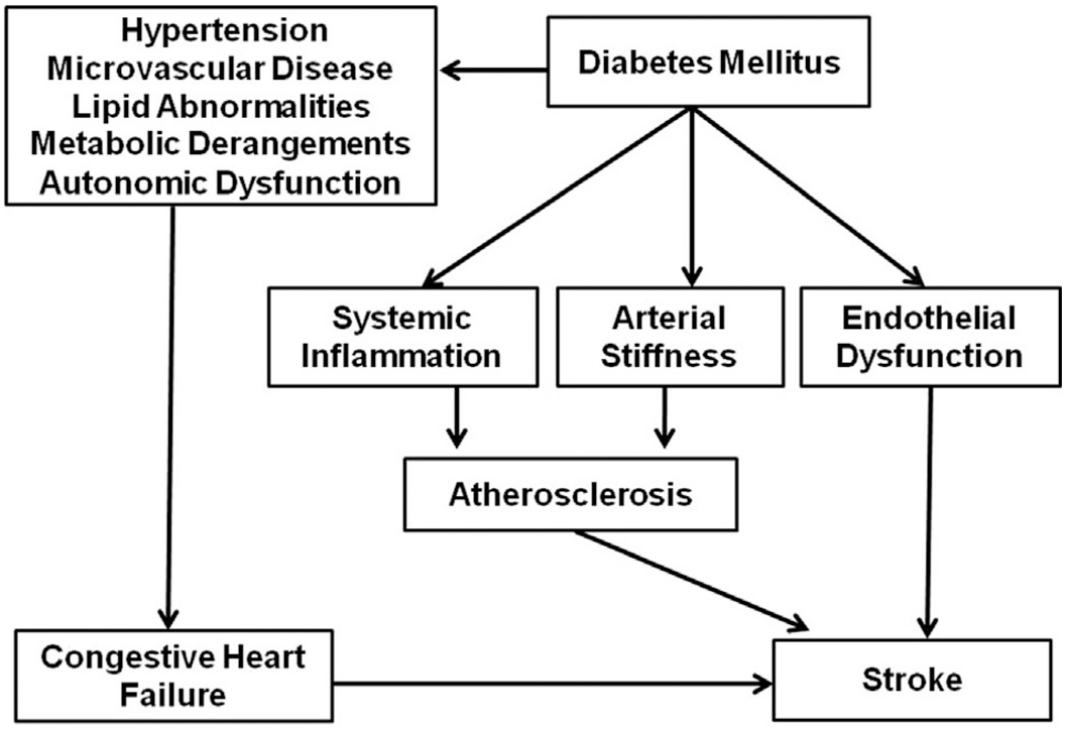


Figure 8

Possible Mechanisms of Stroke in Individuals with Diabetes Mellitus.

Note. Chen, R., Ovbiagele, B., & Feng, W. (2016). Diabetes and Stroke: Epidemiology, Pathophysiology, Pharmaceuticals and Outcomes. The American Journal of the Medical Sciences, 351(4), 380–386. https://doi.org/10.1016/j.amjms.2016.01.011

3.6 How is type 2 diabetes mellitus diagnosed?

The tests to diagnose T2DM are still based on the American Diabetic Association (ADA) guidelines of 1997 or the World Health Organization (WHO) National diabetic group criteria of 2006 (Olokoba et al., 2012). These tests for screening and diagnosis are widely available. However, approximately 25% of people with a new DM diagnosis already have a microvascular disease. This suggests that they have had the disease for 4-7 years by the time of diagnosis (Edelman & Cox, 2009; Harris et al., 1992).

Nowadays, many different types of DM screening exist and vary from history-based questionnaires to proteomics-based risk assessments (Edelman & Cox, 2009). There is a major difference between diagnostic testing and screening. The purpose of screening is to differentiate an asymptomatic individual at high risk from an individual at low risk for DM. So, a positive screening test does not mean the subject is suffering from T2DM, it only means that this subject is more likely to have the disease than a subject with a negative screening test. That is why after a positive screening test, separate diagnostic tests are required to confirm a

definitive positive diagnosis (Engelgau et al., 2000). Identification of patients with a positive screening test allows an earlier intervention. Potentially, there will be a reduction in further complication rates, however, according to a study by Bayness in 2015, some randomised trials have not shown some definitive benefits (Baynes, 2015).

The current diagnostic tests are subdivided into two groups, serum glucose-based, and glycated proteins, haemoglobin A1c (HbA1c), based tests. Serum glucose-based tests include fasting plasma glucose (FPG), random plasma glucose (RPG), and the oral glucose tolerance test (OGTT). The most well-studied and useful glycated protein test is HbA1c (Edelman & Cox, 2009).

3.6.1 Fasting plasma glucose

The FPG is an easy, inexpensive, and relatively risk-free option for screening and diagnosis. The downsides of this test are that it requires patients to fast for eight hours, which can be imperfectly done. Another disadvantage of FPG is that the blood sample processing must be prompt, less than two hours after collection, or the results can be falsely low. And, although the intra-individual stability of FPG is fair, it should be confirmed on a second test to avoid false results. This type of test is also highly correlated with T2DM complications, particularly DR (Edelman & Cox, 2009).

3.6.2 Random plasma glucose

The RPG test measures a patient's blood glucose level at any given point in the day. This test is useful for people who need a speedy diagnosis. Doctors use the results of this test to determine whether a person is likely to have DM. Another test may be necessary to confirm a full diagnosis of DM (Rhee & Barrell, 2022).

3.6.3 Oral glucose tolerance test

Sometimes, patients with DM can still demonstrate normal results in the RPG or FPG, but yet have DM. If a doctor suspects that this person has DM, he will recommend an OGTT. This test also requires that a person fast for eight hours. After an initial blood sample, the patient must drink a liquid containing glucose. The doctor then takes more blood samples hourly over the next two hours (Rhee & Barrell, 2022).

3.6.4 Glycated proteins - HbA1c

Approximately from 2010, a new measurement has been used, haemoglobin A1c (HbA1c). HbA1c is a measure of the average glycaemia over the previous 8 to 12 weeks. It has been recommended as an alternative measurement for the diagnosis of T2DM by the ADA, and the WHO (L. Chen et al., 2011; Sherwani et al., 2016).

In individuals who are not diagnosed with T2DM, an increased HbA1c level is associated with future risk of T2DM, substantially increased risk of the development of adverse cardiovascular events (CVEs), and stroke in subjects who may already have DM (L. Chen et al., 2011; Santos-Oliveira et al., 2011; Sherwani et al., 2016).

High levels of HbA1c are associated with an increased risk of recurrence of atrial tachyarrhythmia in patients with T2DM and paroxysmal atrial fibrillation. Among patients diagnosed with T2DM, even an increase of 1% in HbA1c concentration was associated with about a 30% increase in all-cause mortality and a 40% increase in cardiovascular or ischemic heart disease mortality. Whereas reducing the HbA1c level by 0.2%, could lower mortality by 10% (Sherwani et al., 2016). Research has shown that improving glycaemic control in T2DM patients may be as important as, or even more important than, treating hypertension and dyslipidaemia for the prevention of both micro- and macrovascular complications (Vaag, 2006).

3.6.5 Cytokines

Inflammation plays a major role in the pathogenesis of DR. In different stages, chronic low-grade inflammation has been detected. According to a study by Schröder et al. (1991), activated leukocytes can cause microvascular occlusions and cell damage by the release of cytotoxic products. In 2011, research by Suzuki et al. showed that there is a correlation between cytokines and chemokines, to vascular endothelial growth factor (VEGF) in the vitreous fluid (Suzuki et al., 2011).

In addition to VEGF, anti-inflammatory cytokines may also be involved in the pathogenesis of DR (Suzuki et al., 2011). Furthermore, inflammatory cytokines such as tumour necrosis factor alpha (TNF-α), interleukins (IL) 6 and 8 (IL-6 and IL-8), and interleukin 1-bèta were significantly upregulated in DM patients. Research has shown that their expression level was correlated with the severity of DR (Koleva-Georgieva et al., 2011). Although further research is needed, it seems that C-Reactive Protein (CRP), IL-6, and TNF-α are predictors of increasing morbidity in prediabetic and diabetic patients. According to R.B. Goldberg, the focus of further research should be testing the clinical utility of the levels of anti-

inflammatory cytokines to identify high-risk individuals as well as perhaps to target interventions (Goldberg, 2009).

Presumed, retinal glial cell dysfunction is also involved in the initiation and amplification of retinal inflammation in DR. Retinal glial cells include astrocytes, Müller, and microglia cells. These cells are responsible for providing structural support and maintaining homeostasis in the retina. Hyperglycaemia leads to stress, which activates the microglia cells. This is followed by increasing secretion of proinflammatory cytokines. The amplification of inflammation responses by producing this type of cytokines is associated with the later involvement of Müller cells and astrocytes (Sorrentino et al., 2016; Wang & Lo, 2018).

This type of diagnosis needs to be further researched to be valid.

3.7 What are the common treatments for type 2 diabetes mellitus?

To decrease the prevalence of T2DM, many different attempts have been made. Unfortunately, serious success has still never been achieved. The regular treatments for this disease can be subdivided into pharmacological and non-pharmacological treatments (Khursheed et al., 2019).

3.7.1 Lifestyle modification

According to Olokoba et al., the primary focus must be on the non-pharmacological treatment self-management. Self-management includes diet management and doing exercises (Olokoba et al., 2012). Studies have shown that there was a significant reduction in the incidence of T2DM through weight loss, regular exercise, modification of diet, abstinence from smoking and the consumption of limited amounts of alcohol. Weight control would appear to offer the greatest benefit (Hu, Manson, et al., 2001). This suggests that the majority of patients suffering from T2DM can prevent it by lifestyle modification, and for this reason, lifestyle modifications can be seen as the best cost-effective way for preventing T2DM.

Nutrition advice is recommended for patients diagnosed with T2DM. Weight loss, an important component, can improve blood glucose levels, and positively impacts blood pressure and cholesterol levels. However, patients should be informed of the possible side effects of dieting, such as hypoglycaemia (Chaudhury et al., 2017). In 1992, Riccardi and Rivelesse showed that the consumption of complex dietary fibres and whole grains improve glycaemic control (Riccardi & Rivellese, 1992).

3.7.2 Pharmacological

The pharmacological therapy includes some blood glucose level decreasing agents. According to a study by Seino et al. in 2015, these medicines are vital for the maintenance of glycaemic control in addition to the improvement of lifestyle measures (Al-Nozha et al., 2016). The available pharmacological therapies depend on one or a combination of the pathophysiological mechanisms causing T2DM. According to Chaudhury et al. these mechanisms include:

- "Decreased production and secretion of insulin from bèta-cells of the pancreas;
- Increased production of glucagon from α-cells of the pancreas;
- Dysfunctions in neurotransmission and IR in the brain;
- Increased glucose synthesis by the liver;
- Increased fat and lipid breakdown;
- Increased reabsorption of glucose by the kidneys;
- Reduced uptake of glucose in peripheral tissues like liver, adipose tissue and skeletal muscle;
- Reduced effect of incretin in the small intestine" (Chaudhury et al., 2017).

Using pharmacological therapies can have a disadvantage, because these drugs may have various side effects, such as losing weight due to hyperinsulinaemia, and weakness (Pandey et al., 2011).

3.8 What are the alternative treatments for type 2 diabetes mellitus?

Many studies have been done on alternative therapies for anti-diabetic activity, particularly in India and China. An ideal therapy should have a similar degree of efficiency, but without the bad side-effects of the conventional anti-diabetic drug treatments.

3.8.1 Medicinal herbs

One of these alternative treatments is medicinal herbs. Nearly 60-80% of the world's population uses traditional medicines, which are derived from medicinal plants for various diseases including DM (Khursheed et al., 2019). Over 400 traditional plant treatments for DM have been described. Although only a small number of these treatments have received scientific and medical evaluation to assess their efficiency. For some herbal extracts, the antihyperglycaemic effects have been confirmed in humans diagnosed with T2DM (Dey et al., 2002).

3.8.2 Mineral supplementation

It has been proven that supplying patients diagnosed with T2DM with additional key nutrients will improve blood sugar control. Besides, it helps prevent many major complications of DM (Dey et al., 2002; Mitri et al., 2011; Offenbacher & Pi-Sunyer, 1980). The key nutrients to treat T2DM are:

- Chromium;
- Vitamin D supplementation;
- Vanadium;
- Magnesium.

3.8.3 Probiotics

The definition of probiotic is "for life", which describes the group of various bacterial species exerting beneficial effects on human health. As described, the composition of gut microflora has been implicated as a major factor in the pathogenesis of T2DM. Probiotics may, when given in suitable quantities, bestow beneficial health effects to the host. Probiotics consist of a single, or a collection of multiple species of certain bacteria, and have the capability to improve and modify the indigenous gut flora (Cremon et al., 2018; Isolauri et al., 2004; Khursheed et al., 2019; Schrezenmeir & de Vrese, 2001).

Probiotics enable the synthesis of SCFA, which reduces the intestinal permeability of the endothelial gut wall by enhancing the tight junction proteins (Khursheed et al., 2019).

3.8.4 Prebiotics

According to Snelson et al. (2021) prebiotics can be defined as "substrates which are selectively used by the host bacteria bestowing a health benefit". Prebiotics are food substances which are resistant to digestion and cannot be metabolised or absorbed during their passage through the GIT. These are fermented by the bacterial species residing in the gut and are involved in the improvement of these useful bacteria in the digestive system. Khursheed et al. said in their study "prebiotics can improve human health by three characteristics:

1. Gastric acidity resistance, GIT absorption and hydrolysis by mammalian enzymes;
2. Fermentation by intestinal microflora, leading to the production of SCFAs;
3. Selective enhancement in the expansion and/or activity of gut bacteria" (Khursheed et al., 2019).

So, prebiotics are a special form of dietary fibres and nourish the probiotic bacteria, which are needed to keep our GIT healthy. Unlike probiotics, which are

living bacteria that are intended to help keep the colon healthy (Khursheed et al., 2019).

3.8.5 Synbiotics

Synbiotics are a combination of prebiotics and probiotics. In synbiotics, pre- and probiotics work mutually to have beneficial synergistic effects. Synbiotics stimulate the metabolism of health-sustaining bacteria (Khursheed et al., 2019; Schrezenmeir & de Vrese, 2001).

3.8.6 Miscellaneous approach

Four miscellaneous approaches to treat DM2 have been described by Pandey et al.. (2011). These ways of treatment are:

- Aromatherapy;
- Biofeedback;
- Hydrotherapy;
- Chromotherapy.

3.8.7 Complementary interventions

3.8.7.1 Acupuncture

In 2002, the definition of acupuncture was described by J. Motl as “the branch of traditional Chinese medicine (TCM) that is used to prevent and treat disease by the painless insertion of needles at certain key points in the patient's body”. According to Motl, These points are part of the meridian system that is accepted inside the acupuncture world. (Motl, 2002). In China, acupuncture is a common approach to treating DM and related complications. It may be an effective way to treat not only DM but also in preventing and managing complications of this disease (Dey et al., 2002; Pandey et al., 2011).

There are numerous Chinese publications about acupuncture and DM, but almost all of them have been written in the Chinese language. Unfortunately, these articles were not usable in this study.

Dey et al. (2002) stated in their article about the effects of acupuncture on DM “Acupuncture can act on the pancreas to enhance insulin synthesis, increase the number of receptors on target cells, and accelerate the utilization of glucose, resulting in lowering of blood sugar”. And “It appears that the therapeutic effect of acupuncture on diabetes is not the result of its action on one single organ, but on multiple systems”.

3.9 Osteopathy

3.9.1 What is osteopathy and how does it search for health?

The founder of osteopathic medicine is Andrew Tayler Still ('Andrew Taylor Still', 2022; Muts, 2016). The osteopathic approach is based on expressing the philosophy of osteopathy in a clinical context. Since Still's death in 1917, some efforts had been made to condense his extensive teachings into a comprehensible and concise set of principles. In 1953, a committee of American DOs created a set of guiding principles of the osteopathic approach called the Osteopathic Concepts. This version was limited to only four principles: (Gevitz, 2006; Paulus, 2013)

1. The body is a unit.
2. The body possesses self-regulatory mechanisms.
3. Structure and function are reciprocally interrelated.
4. Rational therapy is based upon an understanding of the body unity, self-regulatory mechanisms and the interrelationship of structure and function.

In 2009, these four key principles were edited into a new interpretation of A.T. Still's philosophy: (Paulus, 2013)

1. The human being is a dynamic unit of function.
2. The body possesses self-regulatory mechanisms that are self-healing in nature.
3. Structure and function are interrelated at all levels.
4. Rational treatment is based on these principles.

The principal point in an osteopathic treatment is "movement is life, and life is movement" (Nijhuis, 2004).

All humans are unique and have their own capacity to resist damage to the human system. There is an interaction between structure and function. If this interaction is disturbed, then symptoms could appear wherever. This can be just in the body, but also in the mind. The symptoms will not always appear at the same place as the loss of motion, because there is not a linear relationship between these two variables. Pain can be seen as overcompensation of the system (Nijhuis, 2004).

The role of an osteopath is to restore balance in the human body and then to ensure this balance. If the balance is restored, the natural vitality will do its work. This mechanism of natural vitality is associated with the capacity of humanity to recover naturally when the body-unit is in balance. When self-regulation is intact, there is immunity, good circulation, and good signal conduction.

The target of an osteopathic treatment is not to treat the symptoms of a patient, or to reduce these symptoms. An osteopath just looks for losses of motion and will

treat these losses. By treating these losses of motion, the total human body-unit will rediscover its equilibrium by itself due to self-regulation. If there is an equilibrium in the body-unit, nature will do the rest. Due to this self-regulation of the human body in equilibrium, the symptoms will disappear on their "own". So, an osteopath will not treat the symptoms or a disease. An osteopath just wants to reactivate self-regulation, by resolving the loss of movement in the human body-unit. Because the release of mechanical blockages, disruption of neurogenic dysregulation, recovery of venous congestion, freedom of the arterial blood flow disturbances, lymphatic and interstitial drainage, and flow of the CSF are important for the restoration of this natural flow.

This means that from an osteopathic point of view according to the philosophy of SCOA, there is not just one cause of T2DM. T2DM is just a symptom and must be seen as an overcompensating body-unit, which consists of the body and mind. This overcompensation leads to symptoms across the body-unit. So, T2DM can be seen as a result of a system in disequilibrium. To correct this imbalance, an osteopath will look for the primary structures which are not mobile and affect the whole system.

In osteopathy, five different models can be used to explain the osteopathic clinician's diagnosis and treatment of a patient. These models are:

- Biomechanical Model;
- Neurological Model;
- Respiratory/Circulatory Model;
- Bio-psychosocial Model;
- Bio-energetic Model.

These five explanatory models can be used to explain the osteopathic mechanism of the origin of T2DM. However, according to the philosophy of SCOA, these models do not influence osteopathic research and OMT. It should only be used afterwards, to explain the mechanism of a given OMT.

A possible explanation for the respiratory or circulatory model is that insulin is carried by blood, lymph and liquor. When the fluid is not "mobile" anymore, the circulation is less and therefore also the reactivity to this insulin. A possible cause for this mechanism can be a restriction of the movement of the abdominal diaphragm because the diaphragm can be seen as a lymphatic pump (Kocjan et al., 2017). Another drawback of less "mobile" fluid is that low-grade inflammation will not quickly be combated. Ultimately, this can lead to IR. Dysfunction of the abdominal diaphragm can be caused by a restriction in C3-C5, due to its innervation (Banneheka, 2008). So, the circulatory system is affected by mechanical dysfunction in this way. The link between these two systems is the nervus phrenicus.

When there is a dysfunction of a structure, there will be reduced drainage of this structure. Dysfunction of the pancreas can be caused by any other related structure due to its biomechanical or neurological relationships. This reduced mobility can lead to reducing drainage. Consequently, the low-grade inflammation can continue, which ultimately leads to IR.

All of these five models are connected to eachother. A problem in one model has some effect on every other model. If somewhere in the body-unit a link goes wrong, a chain reaction will develop.

The philosophy of OMT could also be used for treating patients suffering from T2DM. Currently, there are only a few studies that assessed the relationship between T2DM and OMT. These studies suggested a relationship between these two, but could not assure the true effect. This is caused by a lack of direct investigation of the two components together or low quality of papers.

A possible mechanism of an OMT for a patient suffering from T2DM is that treatment can influence the drainage of the abdominal mass. This causes a change in local homeostasis including the small intestine, and colon. Due to the increased removal of waste products, low-grade inflammations are inhibited. Theoretically, this can inhibit the development of IR.

However, OMT inhibits not only the inflammations in the small intestine and colon, but can also inhibit some inflammations in other places. Like in the pathogenesis of DR or DN. So, it should also have some effects on the inhibition of the complications of T2DM.

3.9.2 Research questions:

Considering the possible (positive) influence of an OMT to patients suffering from T2DM, our university, SCOA, would like to start with a large-scale study to give an answer to the following important question:

Research question:

- Does osteopathic manipulative treatment have an effect on type 2 Diabetes Mellitus patients?

To answer this question, the following sub-questions have been used:

- Are there specific osteopathic techniques or organs that are commonly used/treated in T2DM patients in the available literature? If so, is there any effect?
- Is the available literature on the effect of OMT on type 2 diabetes mellitus valid?

To answer the above questions, we will find out what kind of comparative studies have already been done, assessing their quality and extracting the essential information.

Our research hypothesis is that OMT have a positive influence on the measured parameters of T2DM patients.

4. Method

Kitson et al. (1998) defined evidence as the combination of research, clinical expertise and patient choice.

A gradual movement has been seen in the last decade toward clinical care based on research evidence (Sackett et al., 1996). This concept of evidence-based medicine and more inclusively, evidence-based practice (EBP) is explained as the combination of the best available research evidence with clinical expertise (Sackett, 2000).

Osteopathy has deep roots and has been practised since 1874 (DiGiovanna et al., 2005). Clinical decision-making is embedded within traditional concepts and principles. Current research brought some writers to question the validity and usefulness of those models (Sundberg et al., 2018), and McGrath (2015) even declared that “the days of so-called opinion-based practice have truly passed”.

4.1 Inclusive and exclusive criteria

To obtain the studies that are within the limits of this research, the databases and journals were searched using specific keywords. Besides, inclusion and exclusion criteria have been defined.

4.1.1 Inclusion

In most databases or journals the following keywords search was applied: "Diabetes mellitus" OR "Diabetes type 2" AND "osteopathic treatment" OR "osteopathic manipulative treatment".

In the other databases, a wider search was applied due to the limitations of the search engines. This is shown in table 4.

- Ethnicity: no limitation was implied;
- Every comparative study;
- Abstract in English;
- All languages that are possible to be translated with Google translate;
- Studies that are within the authors’ financial and time resources correspond and can therefore be procured.

Table 4

The Website's Search with all Included And Excluded (in brackets) Articles.

Source	Search terms	Search outcome	Exclusion after Reading title	Exclusion after Reading abstract
Google Scholar	"Diabetes mellitus" OR "Diabetes type 2" AND "osteopathic treatment" OR "osteopathic manipulative treatment"	136	5 (-132)	0 (-5)
PubMed	"Diabetes mellitus" OR "Diabetes type 2" AND "osteopathic treatment" OR "osteopathic manipulative treatment"	145	3 (-142)	0 (-3)
Chocrane Library	"Diabetes mellitus" OR "Diabetes type 2" AND "osteopathic treatment" OR "osteopathic manipulative treatment"	844	1 (843)	0 (-1)
International Journal of Osteopathic Medicine	Diabetes	38	4 (-34)	1 (-3)
The Journal of the American Osteopathic Association	Diabetes and treatment and osteopathy and OMT	35	0 (-35)	0
Akademie Für Osteopathie	Diabetes	0	0	0
Osteopathic research web	Diabetes	25	8 (-18)	2 (-7)
Osteopathic Medical Digital Repository	"Diabetes mellitus" OR "Diabetes type 2" AND "osteopathic treatment" OR "osteopathic manipulative treatment"	327	2 (-325)	1 (0)

Science direct	"Diabetes mellitus" OR "Diabetes type 2" AND "osteopathic treatment" OR "osteopathic manipulative treatment"	25	0 (-25)	0

4.1.2 Exclusion

The exclusion criteria that have been used in this study were:

- Babies as subjects;
- Animals as subjects;
- Osteopathic physicians (USA).

4.2 Literature search

In this study, the decision that has been taken was to include only comparative studies that are directly related to T2DM and any kind of OMT. Comorbidities of DM have not been searched alone and were not included in this thesis.

From April to June 2022, various journals and search engines were searched. These journals and search engines were:

- Google Scholar;
- PubMed, Cochrane Library;
- International Journal of Osteopathic Medicine;
- The Journal of the American Osteopathic Association;
- Akademie Für Osteopathie;
- Osteopathic research web;
- Osteopathic Medical Digital Repository and Science direct;
- Finally, references from retrieved articles were screened.

A total number of 1575 articles were found. Those articles were screened in the title for relevance to this study. Out of those only 24 articles were applicable. Of 24 articles, only 4 articles were left after the screening of the abstract. Lastly, all duplicates were removed and 3 final randomised control trials (RCTs) remained. These steps are shown in figure 9.

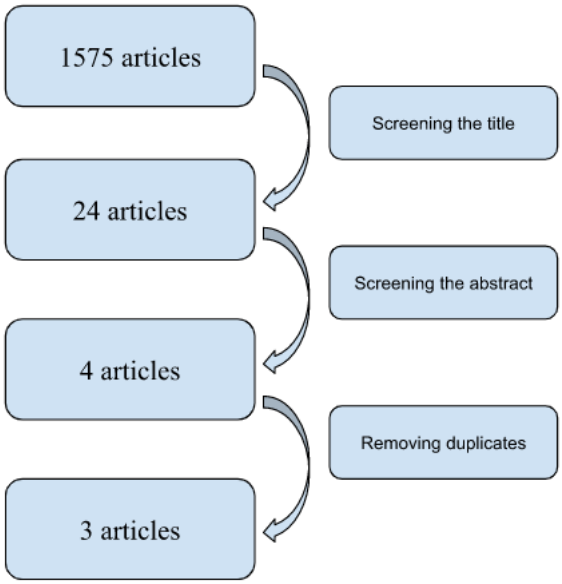


Figure 9
The Literature Search Steps which has been Used in this Study.

4.2.1 Search terms

The search terms we have used are "Diabetes mellitus" OR "Diabetes type 2" AND "osteopathic treatment" OR "osteopathic manipulative treatment".
On some websites, only the word "Diabetes" was searched due to the low number of articles on the website.

The term "Osteopathy" was not included due to many articles about diabetic osteopathy, which relates to osteoporotic processes by diabetic individuals.

4.2.2 Cochrane Library

Of 844 papers we found at the Cochrane Library, there was only one article that looked related to the topic of this thesis. Unfortunately, we could not get access to it.

4.2.3 Osteopathic research web

Only eight articles that could have been relevant were found on the Osteopathic research web. Six of them had a title and abstract, but no full access to the whole paper. To be able to obtain them, we have sent an email to all of the following universities two times:

- Escuela de Osteopatía de Madrid;
- European College of Osteopathy;

- British College of Osteopathic Medicine;
- FICO Osteopathy Academy.

The emails were sent on 3 May 2022 and on 15 June 2022.

4.3 Critical tool: Physiotherapy Evidence Database scale

All three articles that were found were RCTs, therefore the Physiotherapy Evidence Database (PEDro) scale was chosen as a critical tool to evaluate the relevancy of the selected articles. Both authors criticised the articles individually and then compared the scores and discussed the results.

The PEDro Scale has 11 criteria. Every RCT that was criticised received one point for each YES answer that it fulfilled, except the first criterion. Points are only awarded when a criterion is clearly satisfied.

The sum of the fulfilled criteria (YES answers) was counted. This score gives an idea about the internal validity of the research, and if it has sufficient statistical information.
The interpretation of the PEDro scale on the website is 0-3 points considered as "poor", 4-5 "fair", 6-8 "good" and 9-10 "excellent".

4.4 Foreign languages

The authors have sufficient knowledge in the following languages: Dutch, Hebrew and English. One RCT and one literature review, which were included in the study, are written in Portuguese and German respectively and were translated with Google Translate.

5. Results

Three trials met the inclusion criteria. All of these three have tested the effect of OMT on T2DM patients. Each study investigated different parameters to answer this question.

5.1 Pêgas de Oliviera (2005)

In the first study, Pêgas de Oliviera (2005) made a protocol to challenge this question. This protocol focused on mobilization and manipulation of the following structures:
- Sutura occipitomastoidea;
- Dog technique to vertebra T9;

- Diaphragm treatment:
    - Manipulation of C3-C5 bilateral;
    - Diaphragm lift during inspiration and traction during expiration;
- Hepar “pump” - compression of the hepar is performed during inspiration and the pressure is relieved during expiration;
- Gaster mobilization to all directions – indirect mobilization of the pancreas.

From a total of 32 T2DM participants, 15 were assigned to the control group and 17 to the treatment group.

Pêgas de Oliviera chose to investigate those three items:
- Blood glucose levels;
- Blood insulin levels;
- HbA1c value.

Blood samples were taken before the treatment (baseline), and 0 (T0), 15 (T15) and 30 (T30) minutes after the treatment.

A T-test was used to find statistical differences between the two groups. At all times (baseline, T0, T1 and T2) the blood glucose levels were significantly different between the groups (CI 95%, p=2.8e-5, 2.5e-5, 2.7e-7, 9.2e-7 respectively) which indicates a significant decrease in glucose in the blood.

At all times (baseline, T0, T1 and T2), the blood insulin levels were significantly different between the groups (CI 95%, p=.007, .048, .005, .005 respectively) which indicates a significant increase in insulin in the blood. HbA1c value was taken in the baseline only and was not analysed further.

5.2 G. Kiegerl (2006)

In the second study, G. Kiegerl (2006) tested the blackbox method on 10 participants in her thesis. The control group, which was composed of 10 participants as well, was chosen by a general practitioner and further the author stated that she did not know them. The inclusion criteria for the subjects of this study are:
- Non-insulin-dependent diabetics;
- Medicamentously stabilized type-II diabetics;
- Age 45 to 75 years.

And the exclusion criteria are:
- Insulin-dependent diabetics;
- Type-I diabetics;
- Diabetics suffering from other severe diseases, such as apoplectic stroke, myocardial infarct, and multiple sclerosis.

Kiegerl examined not only the effect of OMT but also the consequence of different treatment frequencies between the blood testing intervals.
Two main parameters were checked: HbA1c values and fasting blood glucose.

The HbA1c value of each patient in four moments was assessed:
- T0: On the day of arrival;
- T1: 12 weeks after the first osteopathic treatment (T1);
- T2: 24 weeks after the first osteopathic treatment (T2);
- T3: 36 weeks after the first osteopathic treatment (T3).

Between T0 and T1, 4 OMT-sessions were applied, and between T1 and T2 two sessions were applied. On the other hand, between T2 and T3 no OMT-session was applied.

In this way the author could investigate a couple of parameters;
1. The general effect of OMT on HbA1c.
2. The long-term effect of OMT.
3. Reaction for frequency.

The standard limit is 6,2%, and deviations between the groups from the standard limit are:
- The baseline to T1: decrease HbA1c value by 44.25% in the treatment group and 10.58% in the control group;
- T1 to T2: decrease HbA1c value by 43.36% in the treatment group and 17.46% in the control group;
- T2 to T3: decrease HbA1c value by 30.97% in the treatment group and 10.05% in the control group.

Figure 10 shows the results of the treatments and HbA1c assessment intervals (Kiegerl, 2006).

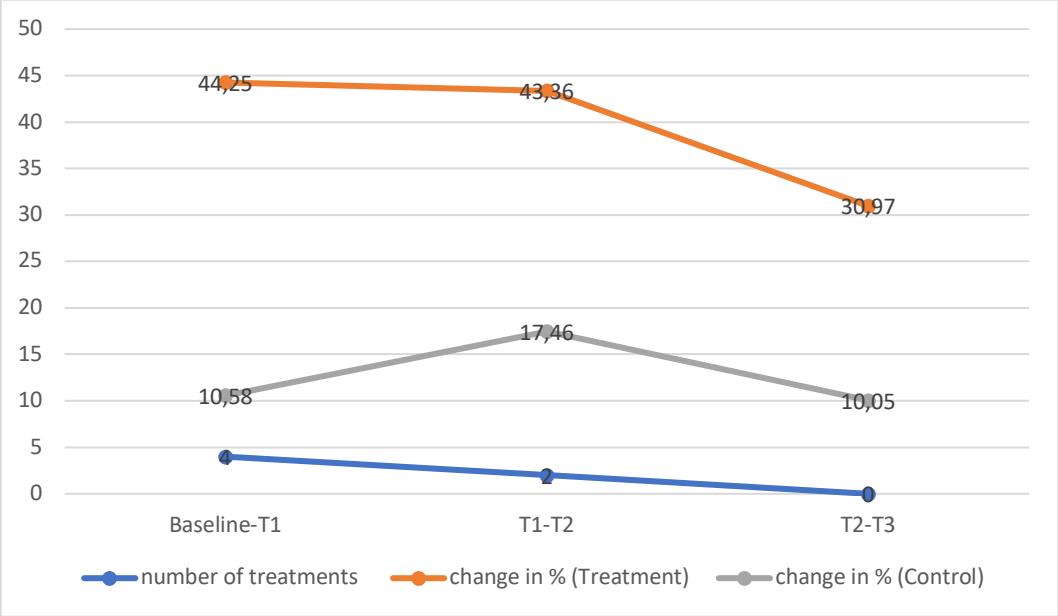


Figure 10

Results of HbA1c in the Study.

Note. All the Orange and Grey lines Indicate the Percentage of Decreased HBA1c Value.

Blood glucose on the other hand was tested in three moments. Those moments were the same as the moments for the HbA1c except for the last test (baseline, T1 and T2). The deviations from the standard limit were:

- The baseline to T1: decrease blood glucose level of 52.97% in the treatment group and 29.47% in the control group;
- T1 to T2: decrease blood glucose level of 18.32% in the treatment group and 6.29% in the control group.

None of the results for both HbA1c value and fasting glucose blood levels was significant.

5.3 Licciardone et al. (2013)

In a different study from 2013, Licciardone et al. wanted to investigate the same question used data from The OSTEOPATHIC Trial, which was conducted by the Osteopathic Research Center between august 2006 and January 2011 (Licciardone et al., 2013). In the data, they tested the effect of OMT and ultrasound therapy (UST) on patients with chronic low back pain. UST results are not presented in this review.

The main measurements were:

- Visual analogue scale (VAS);
- TNF-a serum (was taken only from November 2009).

The measurements were taken:
- Right before the first treatment;
- After 12 weeks.

From the original study, out of 455 participants 34 had DM. The inclusion criteria of participants were:
- Age: 21–69 years;
- Patients who self-reported low back pain on most days during the past three months.

The exclusion criteria were:
- No “red flag” conditions:
    - History of recent low back surgery;
    - Receipt of worker's compensation benefits;
    - Ongoing litigation involving back problems;
    - Medical conditions that might impede OMT (or ultrasound therapy) protocol implementation;
    - Corticosteroid use in the past month;
    - Clinical evidence of lumbar radiculopathy;
    - The presence of ankle dorsiflexion weakness;
    - Great toe extensor weakness;
    - Impaired ankle reflexes;
    - Loss of light touch sensation in the medial, dorsal, and lateral aspects of the foot;
    - Shooting posterior leg pain or foot pain upon ipsilateral or contralateral straight leg raising;
    - Patients who had received manual therapy in the past three months, or more than three times in the past year.

A computer-based process randomly allocates patients to either OMT or sham OMT. Patients and outcome assessors were not informed of treatment group assignments.

At the baseline, the DM group was significantly older than the group without it (Mann-Whitney U test – $P<.001$). Further depression, high disability score (Ronald-Morris disability score) and low quality of life score (SF-36 questionnaire) were measured and found as well significantly different ($P<.001$) compared to the group without DM. TNF-a levels were not significantly different ($P=.79$)

Further in this study, they managed to divide the DM group into two groups; the OMT group (n=19) and the sham OMT group (n=15). The original randomization was successful in attaining comparable groups at the baseline. After OMT, VAS for pain score changes were found significantly different between the groups

(95% Confidence Interval (CI); P=.04) and medium effect size (Cohen d=0.7) based on the Cochrane Back Review Group criteria. Additionally, changes in TNF-a serum were significantly reduced; the between-group changes over a 12-week time were significant (95% CI, p=.03) with a large effect size (Cohen d=2.7) based on the Cochrane Back Review Group criteria. It is important to say that the TNF-a serum changes are driven by only 6 participants (4 in the OMT group and 2 in de sham group).

In the table below, table 5, the number of participants, main measurements and time interval for data collection are presented for each study.

Table 5

The Number of Participants, Main Measurements and Time Interval Per Each Study.

	Kiegerl, 2006	**Licciardone et al., 2013**	**Pêgas de Oliveira, 2005**
Number of participants	20	34	32
Measurement	⁎HbA1c value ⁎Fasting blood glucose	⁎VAS ⁎TNF-a serum IL-1beta, -6, -8, -10	⁎Blood glucose ⁎Blood Insulin ⁎HbA1c value
Time intervals	Baseline 12 weeks 24 weeks 36 weeks	Baseline 12 weeks	Baseline, Right after the treatment, 15 minutes after, 30 minutes after

All RCT's were found and criticised with PEDro scale. Table 6 presents the results for this scale with every criterion and its answer.

The articles of Licciardone et al. (2013) and D. André Pâgas de Oliveira C.O (2005) scored 5 out of 10 points whereas the article of G. Kiegerl (2006) scored 3 out of 10 points.

Table 6

The Results of the PEDro Scale.

Criteria	Kiegerl, 2006	Licciardone et al., 2013	Pêgas de Oliveira, 2005
Eligibility criteria were specified	Yes	No	Yes
Subjects were randomly allocated to groups	No	Yes	Yes
Allocation was concealed	No	No	No
The groups were similar at baseline regarding the most important prognostic indicators	No	No	Yes
There was blinding of all subjects	No	Yes	Yes
There was blinding of all therapists who administered the therapy	No	Yes	No
There was blinding of all assessors who measured at least one key outcome	No	Nee	No
Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	Yes	No	Yes
All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	No	No	No
The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Yes	Yes
The study provides both point measures and measures of variability for at least one key outcome	Yes	Yes	No

Total PEDro score	3	5	5

6. Discussion

6.1 The major findings

The aim of this paper is to answer the question "Does osteopathic manipulative treatment have an effect on type 2 Diabetes Mellitus patients?" by doing a literature review.

Firstly, the next two sub-questions will be answered.

- Are there specific osteopathic techniques or organs that are commonly used/treated in type 2 diabetes mellitus patients in the available literature? If so, is there any effect?
- Is the available literature on the effect of OMT on type 2 diabetes mellitus valid?

6.1.1 Sub questions

6.1.1.1 Are there specific osteopathic techniques or organs common treated by OMT in T2DM patients in the available literature? Does it have a positive effect?

From all three used articles, only one specified the used techniques. For this reason, no conclusion can be taken. To have a statement over a result of a specific technique it needs to be applied by more studies for the purpose of comparison. The diaphragm was the only shared structure to be treated in both Kiegerl and Pêgas de Oliveira theses. However, both authors addressed multiple structures at the same treatment session and it is unknown if they applied different treatment techniques for the same structures. Therefore, it is difficult to conclude the treatment effectiveness on this specific structure.

However, according to the osteopathic philosophy of SCOA, there is not just one treatment for a disease. Every patient has to be treated as a whole instead of treating only one, or a few, structures which have been defined before.

6.1.1.2 Is the available literature on the effect of OMT on T2DM valid?

After reviewing all available literature, all three articles had some different parameters to assess the same question. All three articles stated that there is a positive effect of OMT on T2DM though the quality of the data analysing in all of the articles is questionable. Consequently, the validity of the articles is also

questionable. In Pêgas de Oliveira thesis the baseline point of results was significantly different for both blood insulin level and blood glucose level. The data that the research of Liccairdone et al. (2013) was based on the baseline parameters between the control and therapy group was not the same. The therapy group was significantly older (P<.001) and the depression level, disability score and quality of life (QOL) were as well significantly different (P<.001) than the control group. In the third study, by Kiegerl (2006), the author didn't use statistics tools for the data analysis, therefore the results cannot be accounted as significant.

6.1.2 Main research question

In all three articles, the authors stated that a positive effect of OMT on T2DM patients was noticeable. Nevertheless, with respect to these outcomes, the quality of all three articles is questionable. From 24 final articles that were found only three are RCTs on the relevant topic, whereas the other suggest connections between diabetes and osteopathic treatment or diagnosis. All articles scored low which put them between "poor" and "fair" on the PEDro scale.

In her study, Kiegerl found that osteopathic treatment positively influenced diabetic patients, moreover the biggest improvement was in the interval with more OMT sessions. The long-term effect seems to be difficult to investigate due to the necessity of full cooperation from the tested subjects. Despite the fact that Kiegerl found OMT effective in treating diabetic patients, the study group was small (20 individuals) and the significance of the results was not inspected.

Mobility of the spinal vertebrae, organs and cranium was also tested at the baseline stage, but due to the lack of follow-up in this field, the authors have decided not to speak on the findings here.

In a slightly bigger study group, consisting of 32 individuals, André (2005) observed the short-term effects in blood glucose, plasma insulin levels and HbA1c in response to a single osteopathic treatment.

The results showed a significant short-term effect in any time interval where blood glucose decreased and insulin level increased. That might suggest better conduction of the autonomic nervous system towards the organs and an increasing function of the pancreas to secrete more insulin to the blood circulation. HbA1c levels were taken without being analysed, therefore it was not clear for which purpose it has been done.

In contrast to Kiegerl and Liccairdone who used the blackbox method, Pêgas de Oliveira built a treatment protocol based on theoretical reasoning. This protocol can be found in the results section.

The author explained how each technique can influence the body to reach the desired effect.
The focus was:

- Creating more space for N. X at the jugular foramen, skull exit point of this nerve (sutura occipitomastoidea);
- To improve nerve conduction and the mobility of the diaphragm. (Diaphragm mobilization and C3,4,5 manipulation);
- Improving hepar functions in regulating glucose and lipids metabolism (hepar pump);
- Improving pancreas functions in regulating blood glucose (gaster mobilisation).

The significance of his results is questionable as well due to the baseline point results that were statistically significantly different. A baseline point between groups is supposed to try to be identical as possible to be able to test the intervention changes.

In comparison with the other two studies, Liccairdone et al. (2013) did not observe the blood sugar and insulin levels but the change in cytokine serum concentration (IL-1β, IL-6, IL-8, IL-10 and TNF-α) and pain. The possible relationship between cytokine and DM is explained in the introduction. Those markers can indicate prediabetic or diabetic conditions (Koleva-Georgieva et al., 2011; Suzuki et al., 2011). This study was conducted from data that was acquired from previous research which tested the efficacy of OMT in chronic low back pain (Licciardone et al., 2013). Liccairdone et al. (2013) found a subgroup of 34 diabetes patients out of the 455 total participants, extracted and analysed the information specifically for this group with an outcome that OMT can significantly lower the severity of low back pain in patients with diabetes and there is a possible mechanism which reduces circulating levels of TNF-α. Unfortunately, only this significant reduction was found in a small sample of 4 patients. TNF-a measurements were started to be obtained only on November 2009, therefore is a lack of data on that measurement item.

This article had a major limitation as the patients could have T1DM or T2DM due to a lack of specificity in the intake questionnaire for diseases. This study was eventually included in this review but it is important to be aware of that fact.
In 2008, Licciardone wrote in his article about the re-analysis of raw data from 1949 that Bandeen collected over 25 years. Bandeen's data demonstrate a rapid increase of blood glucose levels at 30 and 60 minutes following pancreatic inhibition in 40 non-diabetic patients. Moreover, in his study, Bandeen tested the glucose level in 150 diabetic and non-diabetic patients after pancreatic stimulation with results that indicate rapid declines in blood glucose (Bandeen, 1949). The major limitation of this article is the collection year of the data. In 1949 the standards were different in concern to identify who is diabetic and there was no

differentiation between type I and T2DM. Moreover, the data was nowhere to be found, which forced this review to base its findings only on the re-analysation of Licciardone.

6.2 The meaning of the findings

The available literature on the internet shows only a small amount and relatively low-quality research that has been conducted. All three RCTs have received a score that associates with "poor" and "fair" quality in the PEDro scale which can indicate low to fair validity and/or low to fair statistical information.

In a German systemized review from 2017, Denise Bertl also searched for a connection between osteopathy and diabetes from a slightly different perspective. She stated in her review that "A large number of studies and papers were found, however, it often lacked an osteopathic connection" (Bertl, 2017).

Notwithstanding the low number of articles, many questions are rising from the criticized articles.

6.2.1 Parameters

In every article, the author chose a different parameter to test. André Pêgas de Oliveira and Gabriele Kiegerl choose to investigate the change in HbA1c levels in the blood. Whereas Kiegerl tested the changes during a period of 36 weeks, Pêgas de Oliveira's interval time was remarkably shorter and without a follow-up. HbA1c is an important indicator of average glycemia and risks for complications in DM patients (Little & Rohlfing, 2013); therefore, a positive change in the HbA1c levels might indicate a lower chance to have future complications and better homeostasis.

Licciardone preferred to focus on the change in the cytokine serum concentration and pain.

A small study of 30 subjects showed significant high concentrations of IL-8 in T2DM patients (Esposito et al., 2003). In a different small-scale study of 50 subjects, the hypothesis that TNF-α may be involved in the aetiology of IR in T2DM was embraced by the authors (Swaroop et al., 2012). Koleva-Georgieva et al. (2011) said that cytokines correlate with the presence and severity of diabetic retinopathy. For those reasons, a positive change in blood cytokines level can indicate a positive effect on the DM severity in a particular patient.

6.3 Another vision for the connection between osteopathy and type 2 diabetes mellitus

Johnson and Shubrook (2013) explained how student osteopaths are taught and expected to know the viscerosomatic reflexes of each internal organ; for example, the innervation of the pancreas is between T5 and T9. With that knowledge, the assumption is that due to the dual innervation of the viscera and somatic tissue, somatic dysfunctions can be observed as a manifestation of a disease.

In a different case study that the authors came across, Licciardone tested the palpatory finding with T2DM. The result was that there is an association between T2DM and the right side of T11-L2 (Licciardone et al., 2013). Later, Nelson et al. (2021) conducted research with 40 diabetic subjects to test the correlation between objectively quantified palpatory in tissue changes and blood sugar levels. The patient's posterior cervical spine was palpated in contrast to Licciardone et al., who tested levels T5 to L2, and the results show that palpatory discrimination exists.

6.4 Evidence based practice and Sutherland college of osteopathy

A balanced mix of research-based, knowledge-based and patient experience guarantees the improvement of manual osteopathic practice (Bordoni, 2019). Therefore all three aspects are crucial for the development of this field. In a study from 2020, Ménard et al. proposed that research needs to be conducted on many themes related to osteopathic care beliefs and knowledge; by validating or disproving them to initiate a pool of clinical evidence (Ménard et al., 2020).

In its school vision, SCOA set to itself evidence-informed practice and practice-based evidence as an important base that needs to be introduced and implanted by every student.

Bordoni said that "EBP is definitely a strategy to implement the importance of the manual approach and to have a suitable tool for a comparison with other health figures". Not only for that reason EBP is important; to be able to offer the best patient-centred treatment is vital.

6.5 Limitations

6.5.1 Limited search terms

Due to the strict search method which searched for the direct connection between T2DM and OMT, it is possible that some information was unrevealed. More knowledge could have been gained from searching the effect of osteopathy on the complications of T2DM; this decision was made for the reason that OMT treats the whole person and not a single complication of a disease.

6.5.2 Criticising tool

One of the major components of a systematic review is using a tool for evaluation of the methodological quality of risk of bias (Marušić et al., 2020). In this study, only one tool was chosen to criticise the RCTs in this study. A couple of studies challenged the validity of this scale and stated that it is acceptable and has sufficient reliability for use in systematic reviews of RCTs (de Morton, 2009; Maher et al., 2003; Yamato et al., 2017). Moreover, it seems that it gives a more extensive measure of methodological quality than the Jaded score in stroke rehabilitation literature (Bhogal et al., 2005).

One advantage of the PEDro scale is its website which provides access to a range of appraisal resources. Licciardone's article was available with its criticizing score on its website.

The interpretation of the PEDro scale on the website is 0-3 points considered as "poor", 4-5 "fair", 6-8 "good" 9-10 "excellent". It is cardinal to understand that those classifications have not been validated ('Summary of Measurement Properties of the PEDro Scale', 2019).

The other tools that were not chosen to critique the RCTs were the Jadad score and the apprising tool of the Center for Evidence-Based Medicine (CEBM). The basic Jaded score is composed of five questions. For every question, the RCT can earn half or one point. A score below three indicated a low-quality study.

CEBM appraisal tool has two main sections. The first is the internal validity, which includes nine questions and the second part is the applicability of the study, which contains three questions. A major limitation of this tool is the lack of instructions on how to assign points to each RCT, and therefore no clear cut-off point.

The authors found that PEDro scale has an extended appraisal than the Jadad score and is easier to evaluate than the CEBM appraisal tool. Therefore, they chose it for their review. It is important to note that there are many more appraisal

tools that one can use. The authors chose the above three and from them the one that fit the most.

6.5.3 Language

As mentioned in the method section, the authors have sufficient knowledge in the following languages: Dutch, Hebrew and English. One RCT and one literature review which included in the study are written in Portuguese and German respectively and were translated with Google Translate. Dyah Raina Purwaningsih in her paper said about Google Translate: "Google Translate does have positive sides and it is quite helpful for some people who need a quick translation process. However, as a machine, it cannot maximally result accurate, acceptable, and readable translation because it does not have translation competences which are very important in translating a text" (Purwaningsih, 2016).

6.5.4 Obtaining articles

Six emails have been sent to various universities to obtain some potential articles that were found on the "Osteopathic research web" website. Unfortunately, only two schools replied and attached the necessary article to their email. It might be presumed that more articles are stored in different universities with relevant material for this study. If this knowledge could be shared, the results of the current review might have been different.

Additionally, an attempt to contact Denise Bertl to gain some extra information was made. Unfortunately, without success.

6.6 Suggestions for further research

In this research, the study is done on the available literature about the effectiveness of OMT on patients suffering from T2DM. SCOA wants to start a large-scale research project to prove the effectiveness of OMT to T2DM patients. Therefore, some improvement points are presented for such future study.

6.6.1 Number of participants

All the studies that have been found are small-scale studies with a low number of participants. To gain a more significant research outcome, larger therapy and control groups need to be observed.

To get more patients, it is vital to get a patient flow from a relevant patient association. To set those connection lines is of importance.

Alongside that, we recommend contacts to be made with academics and doctors. So, they can refer patients to SCOA for research. This may benefit the number of participating patients. Moreover, we can use some of their knowledge about this disease.

6.6.2 Duration of research

OMT can have short- and long-term effects. Accordingly, both need to be discovered. From the information presented in this study, OMT helps in both conditions. The short-term effect was tested 30 and 60 minutes after the therapy by Pâgas de Oliveira and Bandeen, while the long-term effect was evaluated from 12 up to 36 weeks post-intervention by Licciardone et al. and Kiegerl respectively. To learn more about the long-term effects of OMT, the post-intervention time of an evaluation must be longer.

6.6.3 Measurement tool

Improvement in one's health condition can be seen from many angles. A person is not only his blood values, but those can indicate a possible positive advance in his physical and mental status. As the person is a dynamic unit of function and the body's structure and function are interrelated at all levels, a battery test needs to be constructed to be able to contain all levels of the structural, functional and emotional changes.

Possible test battery:

- Blood plasma values:
    - HbA1c – long-term effect
    - Blood glucose and insulin – short-term
    - Inflammation markers – cytokine
- Palpation
- Viscerosomatic reflex
- General tissue changes
- Quality of life questionnaires

There might be more possibilities for the test battery which are not covered in this study. Further study should determine whether other measurement methods exist and which method is most useful and reliable. By knowing this, all further research can use the same measurement tools instead of each study making its own. That can open a possibility for meta-analysis research in the future and higher evidence level for osteopathic methods.

6.6.4 Treatment – protocol versus blackbox

Essentially, two types of osteopathic studies exist. The first one is the technique studies. In a technique study, specific osteopathic procedures are performed by the treating osteopath. These studies are valuable to determine the specific effects of well-specified and described manipulation on a target problem. This method can be called open box research, the opposite of blackbox, because all the steps of the research can be described like a protocol and are visible to someone else. The great advantage of this way of research is that someone else can repeat this research to check the results (Müller et al., 2015).

The second type of study is the black box method. This type is designed to make use of the full range of manipulative techniques to treat a targeted problem. The choice of technique depends on the finding of the osteopath in the physical examination. People suffering from the same syndrome may display similar symptoms. According to the black box point of view, the osteopath does not treat all patients in the same way, though he gives every individual person the treatment he needs. In the end, all the results will be compared to each other, without looking at the specific techniques that were applied in the treatment. The major drawback of this way of doing research is that nobody can check the research, because it is not exactly reproducible. This comes at the expense of the reliability of the research (Tramontano et al., 2022). Guidotti et al. (2019) add that blackbox is a research system that hides the internal logic of the method from the user. They agree that this lack of explanation constitutes both a practical and an ethical issue.

It is important to note that in all of the articles which were found OMT was written as the intervention method, despite the difference that is written above.

In his study, Pêgas de Oliveira used a protocol to inspect the effect of OMT. This protocol was built on osteopathic principles. Different techniques were included to facilitate the mobilisation of various structures.

In contrast, Licciardine et al. (2013) and Kiegerl (2006) used the blackbox treatment method. The osteopathic vision focuses on health and how it can be restored if the natural flow is disturbed. Also, the search for symptoms is of lesser importance than the inspection of loss of mobility which can cause them. By solving the loss of mobility balance can be restored, therefore the blackbox method seems more adequate for future research assessing the efficacy of the osteopathic method.

According to the philosophy of SCOA, every patient needs his own treatment. Regardless of the patient's symptoms. An OMT does not depend on the symptoms

of a patient. Because of this, a treatment protocol cannot be used. In this way, the focus of further research must be on the blackbox method.

6.6.5 Complementary medicine

OMT can be seen as complementary medicine. Another complementary medicine which is taught at SCOA is mesology. In the future, a study can be started together with the study of mesology. A possible research question can be: "Has a treatment of mesology in combination with an OMT beneficial effects on patients with T2DM? Furthermore, the study of mesology can also do research on the effects of the treatment of mesology on patients suffering from T2DM.

6.6.6 Data processing

To meet the intended large patient flows, good data processing must be available. Research can be done as to what is the best way to register all the results properly and digitaly. This can be done in cooperation with an online practice management system, like Crossuite.

Moreover, data analyzing software is crucial for finding significant or non-significant results.

6.6.7 Suggestion for further research

As mentioned above, SCOA would like to initiate large-scale research. The aim of this research is to assess the effects of OMT on patients suffering from T2DM. For this purpose, a proper set-up needs to be established.

We have a couple of suggestions that we would like to share.

1. Two similar groups, control and therapy, need randomly to be allocated and being blind to the research.
2. The number of patients needs to be above 80 patients to strengthen the research validity.
3. To be able to reach points 1 and 2, a strong collaboration between SCOA and DM association and/or hospitals needs to be founded.
4. Preferably the treating osteopaths will be blinded as well to the research.
5. The treatment intervals will be identical for all patients. Preferably every 2-3 months.
6. The research will be longer than five years to assess long-term effects.
7. The patients need to be categorized as having type 2 diabetes mellitus by the GP or any medical worker that is authorized to do so.
8. The treatment group will be treated by the "blackbox" method.
9. The placebo group will be treated by a pre-made protocol.

10. The measurement that needs to be taken are:
    a. HbA1c value;
    b. Blood insulin and glucose level;
    c. VAS pain scale;
    d. QOL questionnaires;
    e. Cytokine serum concentration (IL-1β, IL-6, IL-8, IL-10 and TNF-α).

Further research needs to be done on all of these suggestions to get the most valid and reliable research results. For example, every patient needs to be screened for the use of medications. Medications can have an influence on the blood test and therefore alter the end results of the research. Another example is the number of participants (80) in the suggestions, this is not based on any research. So, extensive research needs to be done to be able to understand which number of participants will give the research a strong valid result.

6.6.8 Five explanatory models

Biomechanical, neurological and circulatory models were all implemented with or without the knowledge of the authors from the above RCTs. For example, mobilisation of the pancreas may have a hormonal influence on the level of the cells, a circulatory effect due to the relaxation of the surrounding tissue and a neurological connection through the viscerosomatic reflex. However, these models should not lead the treatment of an osteopath according to the philosophy of SCOA. It should only be used afterwards to explain the consequences of treatment.

Pêgas de Oliveira et al. (2005) used mobilization and manipulations techniques to the skull, spine, diaphragm and visceral structures (hepar, gaster and pancreas) in their protocols. By this he addressed the bio-mechanical, neurological and circulatory models. However, Licciardone et al. and Kiegerl used the blackbox method; therefore, the specific mobilisations and/or manipulations which were applied in their study are unknown. The other two models, bio-psychosocial and bio-energetic, are not assessed and it might be more complete if both will be addressed as well if possible.

7. Conclusion

The aim of this review was to find evidence that examines the effect of OMT on T2DM subjects. First we described briefly DM and T2DM, using amongst all anatomy and physiology of the pancreas. Then we zoomed in on the pathogenesis of T2DM, T2DM's diagnoses', the complications and the general treatments. In the next part we described osteopathy and the existing literature that examines the effect of OMT on T2DM subjects. Some literature speaks directly

on the connection between these two. Most of it is based on theoretical ideas, professional opinion and osteopathic trials on other conditions. Those articles presume a connection but state that more research needs to be done.

All three RCTs who put this question to test, touched it from different angles; all of them concentrated on blood values but each one assessed different parameters within it.

It seems clear from today's literature that HbA1c is a reliable way to test changes in blood sugar levels over 100 days. Even so, diabetes can and needs to be, approached from different directions. Subjective data, such as a patient's quality of life, is of equal importance.

The work of osteopathy can go beyond the intervention and might contribute to the early detection of the risk of diabetes mellitus by palpation. However, the current evidence is too low for concluding that OMT can significantly have an effect on diabetes and the same applies to palpation findings.

Maintaining independence, improving QOL, and avoiding complications and hospital stays are good reasons to put more effort into researching the effect of OMT on T2DM in the future. Thereby, SCOA plans 2022 to initiate the building of a solid foundation for long-term research in a couple of fields; one of them is T2DM. This thesis is the first brick, and further research will help to build a good base for this purpose. Therefore we came up with some recommendations and suggestions in paragraph 6.6.7.

8. Addendum A

8.1 List of figures

9. Addendum B

9.1 List of tables

10. Addendum C

10.1 Literature

Ahmed, A. M. (2002). History of diabetes mellitus. *Saudi Medical Journal*, *23*(4), 373–378.

Al-Nozha, M. M., Ismail, H. M., & Al Nozha, O. M. (2016). Coronary artery disease and diabetes mellitus. *Journal of Taibah University Medical Sciences*, *11*(4), 330–338. https://doi.org/10.1016/j.jtumed.2016.03.005

American Diabetes Association. (2009). Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*, *32*(Suppl 1), S62–S67. https://doi.org/10.2337/dc09-S062

Andrew Taylor Still. (2022). In *Wikipedia*. https://en.wikipedia.org/w/index.php?title=Andrew_Taylor_Still&oldid=099670006

Aronson, D., & Edelman, E. R. (2014). Coronary artery disease and diabetes mellitus. *Cardiology Clinics*, *32*(3), 439–455. https://doi.org/10.1016/j.ccl.2014.04.001

Arvind, K., Pradeepa, R., Deepa, R., & Mohan, V. (2002). Diabetes & coronary artery disease—ProQuest. *Indian Journal of Medical Research*, 163–176. https://www.proquest.com/openview/1c53ee78b5ea6b3b2605663c77ce32c/1?pq-origsite=gscholar&cbl=37533

Bandeen, S. G. (1949). Diabetes: Report covering twenty-five years research on stimulation of pancreas, blood chemical changes. *Osteopath Prof*, *17*(1), 11–15.

Banneheka, S. (2008). Morphological study of the ansa cervicalis and the phrenic nerve. *Anatomical Science International*, *83*(1), 31–44. https://doi.org/10.1111/j.1447-073X.2007.00201.x

Bansal, V., Kalita, J., & Misra, U. K. (2006). Diabetic neuropathy. *Postgraduate Medical Journal*, *82*(964), 95–100. https://doi.org/10.1136/pgmj.2005.036137

Baynes, J. (2015). Classification, Pathophysiology, Diagnosis and Management of Diabetes Mellitus. *Journal of Diabetes & Metabolism*, *06*(5). https://doi.org/10.4172/2155-6156.1000541

Beger, H. G., Warshaw, A. L., Hruban, R. H., Büchler, M. W., Lerch, M. M., Neoptolemos, J. P., Shimosegawa, T., & Whitcomb, D. C. (2018). *The Pancreas—An Integrated Textbook of Basic Science, Medicine, and Surgery*.

Berthoud, H. R., & Jeanrenaud, B. (1979). Acute hyperinsulinemia and its reversal by vagotomy after lesions of the ventromedial hypothalamus in anesthetized rats. *Endocrinology*, *105*(1), 146–151. https://doi.org/10.1210/endo-105-1-146

Bertl, D. (2017). *Diabetes Mellitus in der Osteopathie-Beachten, behandeln, betreuen. Ein Systematisierter Review*. Donau-Universität Krems.

Bhogal, S. K., Teasell, R. W., Foley, N. C., & Speechley, M. R. (2005). The PEDro scale provides a more comprehensive measure of methodological quality than the Jadad Scale in stroke rehabilitation literature. *Journal of Clinical Epidemiology*, *58*(7), 668–673. https://doi.org/10.1016/j.jclinepi.2005.01.002

Bockman, D. E. (1993). *Anatomy of the Pancreas*.

Bordoni, B. (2019). The Benefits and Limitations of Evidence-based Practice in Osteopathy. *Cureus*, *11*(11). https://doi.org/10.7759/cureus.6093

Cecil, R. L. (1908). *A study of the pathological anatomy of the pancreas in ninety cases of diabetes mellitus.* 266–290.

Chandra, R., & Liddle, R. A. (2009). Neural and Hormonal Regulation of Pancreatic Secretion. *Current Opinion in Gastroenterology*, *25*(5), 441 446. https://doi.org/10.1097/MOG.0b013e32832e9c41

Chatterjee, S., Khunti, K., & Davies, M. J. (2017). Type 2 diabetes. *The Lancet*, *389*(10085), 2239–2251. https://doi.org/10.1016/S0140-6736(17)30058-2

Chaudhury, A., Duvoor, C., Reddy Dendi, V. S., Kraleti, S., Chada, A., Ravilla, R., Marco, A., Shekhawat, N. S., Montales, M. T., Kuriakose, K., Sasapu, A., Beebe, A., Patil, N., Musham, C. K., Lohani, G. P., & Mirza, W. (2017). Clinical Review of Antidiabetic Drugs: Implications for Type 2 Diabetes Mellitus Management. *Frontiers in Endocrinology*, *8*. https://www.frontiersin.org/articles/10.3389/fendo.2017.00006

Chen, L., Magliano, D., & Zimmet, P. (2011). The worldwide epidemiology of type 2 diabetes mellitus-present and future perspectives. *Nature Reviews. Endocrinology*, *8*, 228–236. https://doi.org/10.1038/nrendo.2011.183

CHEN, M., BERGMAN, R. N., & PORTE, D., JR. (1988). Insulin Resistance and β-Cell Dysfunction in Aging: The Importance of Dietary Carbohydrate*. *The Journal of Clinical Endocrinology & Metabolism*, *67*(5), 951–957. https://doi.org/10.1210/jcem-67-5-951

Chen, R., Ovbiagele, B., & Feng, W. (2016). Diabetes and Stroke: Epidemiology, Pathophysiology, Pharmaceuticals and Outcomes. *The American Journal of the Medical Sciences*, *351*(4), 380–386. https://doi.org/10.1016/j.amjms.2016.01.011

Cremon, C., Barbaro, M. R., Ventura, M., & Barbara, G. (2018). Pre- and probiotic overview. *Current Opinion in Pharmacology*, *43*, 87–92. https://doi.org/10.1016/j.coph.2018.08.010

D. André Pêgas de Oliveira C.O. (2005). *Verificação de alterações da glicemia e insulinemia em pacientes diabéticos tipo II submetidos a conduta osteopática*.

de Block, J. (2022). *Orgaan- & Verteringsfysiologie*.

de Morton, N. A. (2009). The PEDro scale is a valid measure of the methodological quality of clinical trials: A demographic study. *Australian Journal of Physiotherapy*, *55*(2), 129–133. https://doi.org/10.1016/S0004 9514(09)70043-1

Dey, L., Attele, A. S., & Yuan, C.-S. (2002). *Alternative Therapies for Type 2*

Diabetes. *7*(1), 14.
DiGiovanna, E. L., Schiowitz, S., & Dowling, D. J. (2005). *An Osteopathic Approach to Diagnosis and Treatment*. Lippincott Williams & Wilkins.
Ductus pancreaticus. (2020). In *Wikipedia*. https://nl.wikipedia.org/w/index.php?title=Ductus_pancreaticus&oldid=5452382
Ductus pancreaticus accessorius. (2014). In *Wikipedia*. https://nl.wikipedia.org/w/index.php?title=Ductus_pancreaticus_accessorus&oldid=40366931
Dunning, B. E., Foley, J. E., & Ahrén, B. (2005). Alpha cell function in health and disease: Influence of glucagon-like peptide-1. *Diabetologia*, *48*(9), 1700–1713. https://doi.org/10.1007/s00125-005-1878-0
Edelman, D., & Cox, M. E. (2009, January 1). *Tests for Screening and Diagnosis of Type 2 Diabetes*. American Diabetes Association. https://diabetesjournals.org/clinical/article/27/4/132/1673/Tests-for Screening-and-Diagnosis-of-Type-2
Engelgau, M. M., Narayan, K. M. V., & Herman, W. H. (2000). Screening for Type 2 Diabetes. *Diabetes Care*, *23*(10), 18.
Engerman, R. L. (1989). Perspectives in Diabetes Pathogenesis of Diabetic Retinopathy. *Diabetes*, *38*, 1203–1206. https://diabetesjournals.org/diabetes/article/38/10/1203/8532/Pathogenesi of-Diabetic-Retinopathy
Esposito, K., Nappo, F., Giugliano, F., Di Palo, C., Ciotola, M., Barbieri, M., Paolisso, G., & Giugliano, D. (2003). Cytokine Milieu Tends Toward Inflammation in Type 2 Diabetes. *Diabetes Care*, *26*(5), 1647. https://doi.org/10.2337/diacare.26.5.1647
Falcão, M., Rosas, V., Falcão-Reis, F., Fontes, M. L., Hyde, R. A., Lim, J. I., & Sheth, N. (2022, February 8). *Diabetic Retinopathy Pathophysiology*. EyeWiki. https://eyewiki.aao.org/Diabetic_Retinopathy_Pathophysiology#:~:text=%20Conclusions ,Introduction,in%20working%20middle%2Daged%20adults.
Feldman, E. L., Callaghan, B. C., Pop-Busui, R., Zochodne, D. W., Wright, D. E., Bennett, D. L., Bril, V., Russell, J. W., & Viswanathan, V. (2019). Diabetic neuropathy. *Nature Reviews Disease Primers*, *5*(1), 1–18. https://doi.org/10.1038/s41572-019-0092-1
Ferrannini, E., & Mari, A. (2004). Beta cell function and its relation to insulin action in humans: A critical appraisal. *Diabetologia*, *47*(5), 943–956. https://doi.org/10.1007/s00125-004-1381-z
Fujioka, K. (2007). Pathophysiology of type 2 diabetes and the role of incretin hormones and beta-cell dysfunction. *JAAPA: Official Journal of the American Academy of Physician Assistants*, *Suppl*, 3–8. https://doi.org/10.1097/01720610-200712000-00001
Gevitz, N. (2006). Center or Periphery? The Future of Osteopathic Principles and

Practices. *Journal of Osteopathic Medicine*, *106*(3), 121–129. https://doi.org/10.7556/jaoa.2006.106.3.121
Gittes, G. K. (2009). Developmental biology of the pancreas: A comprehensive review. *Developmental Biology*, *326*(1), 4–35. https://doi.org/10.1016/j.ydbio.2008.10.024
Goldberg, R. B. (2009). Cytokine and Cytokine-Like Inflammation Markers, Endothelial Dysfunction, and Imbalanced Coagulation in Development of Diabetes and Its Complications. *The Journal of Clinical Endocrinology & Metabolism*, *94*(9), 3171–3182. https://doi.org/10.1210/jc.2008-2534
Guénard, F., Deshaies, Y., Cianflone, K., Kral, J. G., Marceau, P., & Vohl, M.-C. (2013). Differential methylation in glucoregulatory genes of offspring born before vs. After maternal gastrointestinal bypass surgery. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(28), 11439–11444. https://doi.org/10.1073/pnas.1216959110
Guidotti, R., Monreale, A., Ruggieri, S., Turini, F., Giannotti, F., & Pedreschi, D. (2019). A Survey of Methods for Explaining Black Box Models. *ACM Computing Surveys*, *51*(5), 1–42. https://doi.org/10.1145/3236009
Gujral, U. P., Pradeepa, R., Weber, M. B., Narayan, K. M. V., & Mohan, V. (2013). Type 2 diabetes in South Asians: Similarities and differences with white Caucasian and other populations. *Annals of the New York Academy of Sciences*, *1281*(1), 51–63. https://doi.org/10.1111/j.1749 6632.2012.06838.x
Gurung, M., Li, Z., You, H., Rodrigues, R., Jump, D. B., Morgun, A., & Shulzhenko, N. (2020). Role of gut microbiota in type 2 diabetes pathophysiology. *EBioMedicine*, *51*, 102590. https://doi.org/10.1016/j.ebiom.2019.11.051
Hansen, M. B. (2003). The Enteric Nervous System I: Organisation and Classification. *Pharmacology & Toxicology*, *92*(3), 105–113. https://doi.org/10.1034/j.1600-0773.2003.t01-1-920301.x
Harris, M. I., Klein, R., Welborn, T. A., & Knuiman, M. W. (1992). Onset of NIDDM occurs at Least 4–7 yr Before Clinical Diagnosis. *Diabetes Care*, *15*(7), 815–819. https://doi.org/10.2337/diacare.15.7.815
Henry, B. M., Skinningsrud, B., Saganiak, K., Pekala, P. A., Walocha, J. A., & Tomaszewski, K. A. (2018). *Development of the Human Pancreas and its Vasculature − An Integrated Review Covering Anatomical, Embryological, Histological, and Molecular Aspects*. https://doi.org/10.1016/j.aanat.2018.09.008
Homsi, M., & Lukic, M. (1993). An Update on the pathogenesis of Diabetes Mellitus. *International Journal of Diabetes and Metabolism*, *1*. https://doi.org/10.1159/000497504
Hu, F. B., Manson, J. E., Stampfer, M. J., Colditz, G., Liu, S., Solomon, C. G., & Willett, W. C. (2001). Diet, Lifestyle, and the Risk of Type 2 Diabetes Mellitus in Women. *New England Journal of Medicine*, *345*(11), 790–797. https://doi.org/10.1056/NEJMoa010492

Hu, F. B., van Dam, R. M., & Liu, S. (2001). Diet and risk of Type II diabetes: The role of types of fat and carbohydrate. *Diabetologia*, *44*(7), 805–817. https://doi.org/10.1007/s001250100547

International Diabetes Federation. (2006). *IDF Consensus Worldwide Definition of the Metabolic Syndrome*. https://www.idf.org/e-library/consensus statements/60-idfconsensus-worldwide-definitionof-the-metabolic syndrome.html

Isolauri, E., Salminen, S., & Ouwehand, A. C. (2004). Probiotics. *Best Practice & Research Clinical Gastroenterology*, *18*(2), 299–313. https://doi.org/10.1016/j.bpg.2003.10.006

Javeed, N., & Matveyenko, A. V. (2018). Circadian Etiology of Type 2 Diabetes Mellitus. *Physiology*, *33*(2), 138–150. https://doi.org/10.1152/physiol.00003.2018

Johnson, A. W., & Shubrook, J. H. (2013). Role of Osteopathic Structural Diagnosis and Osteopathic Manipulative Treatment for Diabetes Mellitus and Its Complications. *Journal of Osteopathic Medicine*, *113*(11), 829 836. https://doi.org/10.7556/jaoa.2013.058

Kahn, S. E. (2003). The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes. *Diabetologia*, *46*(1), 3–19. https://doi.org/10.1007/s00125-002-1009-0

Kahn, S. E., Cooper, M. E., & Del Prato, S. (2014). PATHOPHYSIOLOGY AND TREATMENT OF TYPE 2 DIABETES: PERSPECTIVES ON THE PAST, PRESENT AND FUTURE. *Lancet*, *383*(9922), 1068–1083. https://doi.org/10.1016/S0140-6736(13)62154-6

Kaneto, A., Kosaka, K., & Nakao, K. (1967). Effects of Stimulation of the Vagus Nerve on Insulin Secretion. *Endocrinology*, *80*(3), 530–536. https://doi.org/10.1210/endo-80-3-530

Kaprio, J., Tuomilehto, J., Koskenvuo, M., Romanov, K., Reunanen, A., Eriksson, J., Stengård, J., & Kesäniemi, Y. A. (1992). Concordance for Type 1 (insulin-dependent) and Type 2 (non-insulin-dependent) diabetes mellitus in a population-based cohort of twins in Finland. *Diabetologia*, *35*(11), 1060–1067. https://doi.org/10.1007/BF02221682

Khursheed, R., Singh, S. K., Wadhwa, S., Kapoor, B., Gulati, M., Kumar, R., Ramanunny, A. K., Awasthi, A., & Dua, K. (2019). Treatment strategies against diabetes: Success so far and challenges ahead. *European Journal of Pharmacology*, *862*, 172625. https://doi.org/10.1016/j.ejphar.2019.172625

Kiegerl, G. (2006). *Does Osteopathy influence diabetes mellitus type II* [Donauuniversität Kerms]. https://www.osteopathic research.org/files/original/6a429fa418e58451049ea628fbbfe0f0d945680b pdf

Kitson, A., Harvey, G., & McCormack, B. (1998). Enabling the implementation of evidence based practice: A conceptual framework. *Quality and Safety in Health Care*, *7*(3), 149–158. https://doi.org/10.1136/qshc.7.3.149

Kocjan, J., Adamek, M., Gzik-Zroska, B., Czyżewski, D., & Rydel, M. (2017). Network of breathing. Multifunctional role of the diaphragm: A review. *Advances in Respiratory Medicine*, *85*(4), 224–232. https://doi.org/10.5603/ARM.2017.0037

Kolb, H., & Martin, S. (2017). Environmental/lifestyle factors in the pathogenesis and prevention of type 2 diabetes. *BMC Medicine*, *15*(1), 131. https://doi.org/10.1186/s12916-017-0901-x

Koleva-Georgieva, D. N., Sivkova, N. P., & Terzieva, D. (2011). Serum inflammatory cytokines IL-1beta, IL-6, TNF-alpha and VEGF have influence on the development of diabetic retinopathy. *Folia Medica*, *53*(2), 44–50. https://doi.org/10.2478/v10153-010-0036-8

Lakhtakia, R. (2013). The History of Diabetes Mellitus. *Sultan Qaboos University Medical Journal*, *13*(3), 368–370. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3749019/

Leptine. (2020). In *Wikipedia*. https://nl.wikipedia.org/w/index.php?title=Leptine&oldid=56080553

Li, X. C., & Zhuo, J. L. (2013). Current Insights and New Perspectives on the Roles of Hyperglucagonemia in Non Insulin-dependent Type 2 Diabetes. *Current Hypertension Reports*, *15*(5), 10.1007/s11906-013-0383-y. https://doi.org/10.1007/s11906-013-0383-y

Licciardone, J. C., Kearns, C. M., Hodge, L. M., & Minotti, D. E. (2013). Osteopathic Manual Treatment in Patients With Diabetes Mellitus and Comorbid Chronic Low Back Pain: Subgroup Results From the OSTEOPATHIC Trial. *Journal of Osteopathic Medicine*, *113*(6), 468 478. https://doi.org/10.7556/jaoa.2013.113.6.468

Lippi, D., Caleri, D., Bucalossi, A., & Rotella, C. M. (1994). The role of liver in glucose homeostasis in type 2 diabetes: The modernity of claude bernard's studies. *Diabetes / Metabolism Reviews*, *10*(1), 63–74. https://doi.org/10.1002/dmr.5610100106

Little, R. R., & Rohlfing, C. L. (2013). The long and winding road to optimal HbA1c measurement. *Clinica Chimica Acta*, *418*, 63–71. https://doi.org/10.1016/j.cca.2012.12.026

Longnecker, D. S. (2014). Anatomy and Histology of the Pancreas (Version 1.0). *Pancreapedia: The Exocrine Pancreas Knowledge Base*. https://doi.org/10.3998/panc.2014.3

Ma, Q., Li, Y., Li, P., Wang, M., Wang, J., Tang, Z., Wang, T., Luo, L., Wang, C., Wang, T., & Zhao, B. (2019). Research progress in the relationship between type 2 diabetes mellitus and intestinal flora. *Biomedicine & Pharmacotherapy*, *117*, 109138. https://doi.org/10.1016/j.biopha.2019.109138

Mahadevan, V. (2019). Anatomy of the pancreas and spleen. *Surgery (Oxford)*, *37*(6), 297–301. https://doi.org/10.1016/j.mpsur.2019.04.008

Maher, C. G., Sherrington, C., Herbert, R. D., Moseley, A. M., & Elkins, M. (2003). Reliability of the PEDro Scale for Rating Quality of Randomized

Controlled Trials. *Physical Therapy*, *83*(8), 713–721. https://doi.org/10.1093/ptj/83.8.713
Mankovsky, B. N., & Ziegler, D. (2004). Stroke in patients with diabetes mellitus. *Diabetes/Metabolism Research and Reviews*, *20*(4), 268–287. https://doi.org/10.1002/dmrr.490
Mantzoros, C. S. (1999). The Role of Leptin in Human Obesity and Disease: A Review of Current Evidence. *Annals of Internal Medicine*, *130*(8), 671. https://doi.org/10.7326/0003-4819-130-8-199904200-00014
Marty, N., Dallaporta, M., & Thorens, B. (2007). Brain Glucose Sensing, Counterregulation, and Energy Homeostasis. *Physiology*, *22*(4), 241–251. https://doi.org/10.1152/physiol.00010.2007
Marušić, M. F., Fidahić, M., Cepeha, C. M., Farcaș, L. G., Tseke, A., & Puljak, L. (2020). Methodological tools and sensitivity analysis for assessing quality or risk of bias used in systematic reviews published in the high-impact anesthesiology journals. *BMC Medical Research Methodology*, *20*(1), 121. https://doi.org/10.1186/s12874-020-00966-4
McGrath, M. C. (2015). A global view of osteopathic practice–mirror or echo chamber? *International Journal of Osteopathic Medicine*, *18*(2), 130–140.
Ménard, M., Draper-Rodi, J., Merdy, O., Wagner, A., Tavernier, P., Jacquot, E., & Mhadhbi, H. (2020). Finding a way between osteopathic principles and evidence-based practices: Response to Esteves et al. *International Journal of Osteopathic Medicine*, *37*, 45–47. https://doi.org/10.1016/j.ijosm.2020.07.006
Miller, R. E. (1981). Pancreatic neuroendocrinology: Peripheral neural mechanisms in the regulation of the Islets of Langerhans. *Endocrine Reviews*, *2*(4), 471–494. https://doi.org/10.1210/edrv-2-4-471
Mitri, J., Dawson-Hughes, B., Hu, F. B., & Pittas, A. G. (2011). Effects of vitamin D and calcium supplementation on pancreatic β cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: The Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial. *The American Journal of Clinical Nutrition*, *94*(2), 486 494. https://doi.org/10.3945/ajcn.111.011684
Morioka, T., Asilmaz, E., Hu, J., Dishinger, J. F., Kurpad, A. J., Elias, C. F., Li, H., Elmquist, J. K., Kennedy, R. T., & Kulkarni, R. N. (2007). *Disruption of leptin receptor expression in the pancreas directly affects β cell growth and function in mice*. https://www.jci.org/articles/view/30910
Motl, J. M. (2002). Chapter 20—Acupuncture. In S. Shannon (Ed.), *Handbook of Complementary and Alternative Therapies in Mental Health* (pp. 431 451). Academic Press. https://doi.org/10.1016/B978-012638281-5/500218
Müller, T. D., Nogueiras, R., Andermann, M. L., Andrews, Z. B., Anker, S. D., Argente, J., Batterham, R. L., Benoit, S. C., Bowers, C. Y., Broglio, F., Casanueva, F. F., D'Alessio, D., Depoortere, I., Geliebter, A., Ghigo, E., Cole, P. A., Cowley, M., Cummings, D. E., Dagher, A., … Tschöp, M. H. (2015). Ghrelin. *Molecular Metabolism*, *4*(6), 437–460.

https://doi.org/10.1016/j.molmet.2015.03.005
Muts, R. K. (2010). *Visceraal*.
Muts, R. K. (2016). *Geschiedenis osteopathie*.
Netter, F. H. (2006). *Atlas of Human Anatomy*.
Newman, B., Selby, J. V., King, M.-C., Slemenda, C., Fabsitz, R., & Friedman, G. D. (1987). Concordance for Type 2 (non-insulin-dependent) diabetes mellitus in male twins. *Diabetologia*, *30*(10). https://doi.org/10.1007/BF00275741
Nijhuis, V. (2004). *Principes van de osteopathie*. 7.
Nonogaki, K. (2000). New insights into sympathetic regulation of glucose and fat metabolism. *Diabetologia*, *43*(5), 533–549. https://doi.org/10.1007/s001250051341
Nugent, D. A., Smith, D. M., & Jones, H. B. (2008). A Review of Islet of Langerhans Degeneration in Rodent Models of Type 2 Diabetes. *Toxicologic Pathology*, *36*(4), 529–551. https://doi.org/10.1177/0192623308318209
Obici, S., Zhang, B. B., Karkanias, G., & Rossetti, L. (2002). Hypothalamic insulin signaling is required for inhibition of glucose production. *Nature Medicine*, *8*(12), 1376–1382. https://doi.org/10.1038/nm1202-798
Offenbacher, E., & Pi-Sunyer, X. (1980). Beneficial Effect of Chromium-rich Yeast on Glucose Tolerance and Blood Lipids in Elderly Subjects. *Diabetes*, *29*, 919–925. https://doi.org/10.2337/diabetes.29.11.919
Olokoba, A. B., Obateru, O. A., & Olokoba, L. B. (2012). Type 2 Diabetes Mellitus: A Review of Current Trends. *Oman Medical Journal*, *27*(4), 269–273. https://doi.org/10.5001/omj.2012.68
O'Morchoe, C. C. C. (1997). Lymphatic system of the pancreas. *Microscopy Research and Technique*, *37*, 456–477. https://analyticalsciencejournals.onlinelibrary.wiley.com/doi/abs/10.1002SICI)1097-0029(19970601)37:5/6%3C456::AID-JEMT9%3E3.0.CO;2-B
Opie, E. L. (1901). On the relation of chronic interstitial pancreatitis to the island of Langerhans and Diabetes Mellitus. *The Journal of Experimental Medicine*, *5*(4), 397–428. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2118050/
Ozougwu, J. (2013). The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus. *Journal of Physiology and Pathophysiology*, *4*(4), 46 57. https://doi.org/10.5897/JPAP2013.0001
Pan, F. C., & Wright, C. (2011). Pancreas organogenesis: From bud to plexus to gland. *Developmental Dynamics*, *240*(3), 530–565. https://doi.org/10.1002/dvdy.22584
Pandey, A., Tripathi, P., Pandey, R., Srivatava, R., & Goswami, S. (2011). Alternative therapies useful in the management of diabetes: A systematic review. *Journal of Pharmacy & Bioallied Sciences*, *3*(4), 504–512. https://doi.org/10.4103/0975-7406.90103
Paulus, S. (2013). The core principles of osteopathic philosophy. *International*

Journal of Osteopathic Medicine, *16*(1), 11–16. https://doi.org/10.1016/j.ijosm.2012.08.003

Pêgas de Oliveira, A. (2005). *Verificação de alterações da glicemia e insulinemia em pacientes diabéticos tipo il submetidos a conduta osteopática*. Osteopathic School of Madrid.

Porte, D. (1969). Sympathetic regulation of insulin secretion. Its relation to diabetes mellitus. *Archives of Internal Medicine*, *123*(3), 252–260.

Prakash, S., Rodes, L., Coussa-Charley, M., & Tomaro-Duchesneau, C. (2011). Gut microbiota: Next frontier in understanding human health and development of biotherapeutics. *Biologics : Targets & Therapy*, *5*, 71–86. https://doi.org/10.2147/BTT.S19099

Purwaningsih, D. (2016). Comparing translation produced by Google translation tool to translation produced by translator. *Journal of English Language Studies*, *1*(1), Article 1. https://doi.org/10.30870/jels.v1i1.678.g531

Ravussin, E., & Smith, S. R. (2002). Increased Fat Intake, Impaired Fat Oxidation, and Failure of Fat Cell Proliferation Result in Ectopic Fat Storage, Insulin Resistance, and Type 2 Diabetes Mellitus. *New York Academy of Sciences*, 363–378. https://d1wqtxts1xzle7.cloudfront.net/45684204/j.1749 6632.2002.tb04292.x20160516-12353-1fndsg4-with-cover-page v2.pdf?Expires=1659878506&Signature=N62NjgLPKL1MTAlKsWf3z0 xQEqu1lHwBdIm1enBH70s9VR1E7aIb4Jjyni7eIBoGW5Mobtcsh rGVAj9~EvIOzsQ2Q5 fRDGQzGxOkcW3~IkQ45P65NUCUvYwFp9merSoZvTNW8rijzz~z5a O8GSqcqx02OoADj3ijpI02xK69ahyrKGgxAqHgGvy279XS297CeVtFrl 0voSBxCi2XibSdw5lahSN~hsukZweyjnmuJqooGIRBY85O7MoW~IRb NGkNRT MpwxusqiU~AhsIadMNEp7SbsX3qBzs5Dv0lDzdnhKbd~SVVrGZtIwp icMrtTm4juHRedDL3rzw__&Key-Pair Id=APKAJLOHF5GGSLRBV4ZA

Reichert, M., & Rustgi, A. K. (2011, December 1). *Pancreatic ductal cells in development, regeneration, and neoplasia*. American Society for Clinical Investigation. https://doi.org/10.1172/JCI57131

Rhee, S., & Barrell, A. (2022, March 23). *What is a random glucose test?* Medical News Today. https://www.medicalnewstoday.com/articles/323022

Riccardi, G., & Rivellese, A. (1992). Effects of Dietary Fiber and Carbohydrate on Glucose and Lipoprotein Metabolism in Diabetic Patients. *Diabetes Care*, *14*, 1115–1125. https://doi.org/10.2337/diacare.14.12.1115

Rich, S. S. (1990). *Perspectives in Diabetes Mapping Genes in Diabetes Genetic Epidemiological Perspective*.

Roden, M., & Shulman, G. I. (2019). The integrative biology of type 2 diabetes. *Nature*, *576*, 51–60.

Sackett, D. L. (2000). *Evidence-based medicine: How to practice and teach EBM*. Churchill Livingstone.

Sackett, D. L., Rosenberg, W. M., Gray, J. A., Haynes, R. B., & Richardson, W. S. (1996). Evidence based medicine: What it is and what it isn't. *BMJ (Clinical Research Ed.)*, *312*(7023), 71–72. https://doi.org/10.1136/bmj.312.7023.71

Sadler, T.W. (2015). *Langman's Medical Embryology* (thirteenth). Wolters Kluwer Health.

Salvioli, B., Bovara, M., Barbara, G., Ponti, F. D., Tonini, M., Guerrini, S., Cremon, C., Esposti, M. D., Koum, M., Corinaldesi, R., Sternini, C., & Giorgio, R. D. (2002). *Neurology and Neuropathology of the Pancreatic Innervation*. *3*(2), 26–33. https://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.505.189&rep=ep1&type=pdf

Santos-Oliveira, R., Purdy, C., da Silva, M. P., dos Anjos Carneiro-Leão, A. M., Machado, M., & Einarson, T. R. (2011). Haemoglobin A1c levels and subsequent cardiovascular disease in persons without diabetes: A meta analysis of prospective cohorts. *Diabetologia*, *54*(6), 1327–1334. https://doi.org/10.1007/s00125-011-2078-8

Schlienger, J.-L. (2013). Complications du diabète de type 2. *La Presse Médicale*, *42*(5), 839–848. https://doi.org/10.1016/j.lpm.2013.02.313

Schmidt, M., Duncan, B., Canani, L., Karohl, C., & Chambless, L. (1992). Association of Waist-Hip Ratio With Diabetes Mellitus: Strength and Possible Modifiers. *Diabetes Care*, *15*, 912–914. https://doi.org/10.2337/diacare.15.7.912

Schrezenmeir, J., & de Vrese, M. (2001). Probiotics, prebiotics, and synbiotics Approaching a definition. *The American Journal of Clinical Nutrition*, *73*(2), 361s–364s. https://doi.org/10.1093/ajcn/73.2.361s

Schröder, S., Palinski, W., & Schmid-Schönbein, G. W. (1991). Activated monocytes and granulocytes, capillary nonperfusion, and neovascularization in diabetic retinopathy. *The American Journal of Pathology*, *139*(1), 81–100. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1886150/

Science Encyclopedia. (2022). *Diabetes Mellitus—Incidence Of Diabetes, Types Of Diabetes, Pre-diabetes, Tests For Diabetes, Treatment For Diabetes History of diabetes*. https://science.jrank.org/pages/2044/Diabetes Mellitus.html

Segal, K. R., Landt, M., & Klein, S. (1996). Relationship Between Insulin Sensitivity and Plasma Leptin Concentration in Lean and Obese Men. *American Journal of The Medical Sciences*, *45*, 988–991. https://d1wqtxts1xzle7.cloudfront.net/43153597/988.full-with-cover-page v2.pdf?Expires=1665258725&Signature=ULE4oV6X yQeF3JZs2pQFe4r0ae~aqH4NpFQF6p3ELSwKnm4hEMdF~EyWIqxG qdeCtKhY6Sn003kNj8MtUm1gP-3vzJBtpfU8~F76TS-8wuD8G9glh kzicyYT6SBBQM7NtSZFosYgIFZNcM1bQCf8V7wkFglhHe3NWyOQ KY9yKOwtj9kaQVpegITJRxrdzlaIsuQZlCEQOWbam29FDsicoa8

uBMVlPhzb89Asah9JnsjMD3Ufw7dMALZwAzngOm~Og3rUs4vrBsn XG8gqJkkOaqogbxHITi9SbpBkIjnUe4v~gMrvXuJuq8H4Ta216aKCM H7Fd7siILskw__&Key-Pair-Id=APKAJLOHF5GGSLRBV4ZA

Sherwani, S. I., Khan, H. A., Ekhzaimy, A., Masood, A., & Sakharkar, M. K. (2016). Significance of HbA1c Test in Diagnosis and Prognosis of Diabetic Patients. *Biomarker Insights*, *11*, BMI.S38440. https://doi.org/10.4137/BMI.S38440

Snelson, M., de Pasquale, C., Ekinci, E. I., & Coughlan, M. T. (2021). Gut microbiome, prebiotics, intestinal permeability and diabetes complications. *Best Practice & Research Clinical Endocrinology & Metabolism*, *35*(3), 101507. https://doi.org/10.1016/j.beem.2021.101507

Sohail, M. U., Althani, A., Anwar, H., Rizzi, R., & Marei, H. E. (2017). Role of the Gastrointestinal Tract Microbiome in the Pathophysiology of Diabetes Mellitus. *Journal of Diabetes Research*, *2017*, e9631435. https://doi.org/10.1155/2017/9631435

Sorrentino, F. S., Allkabes, M., Salsini, G., Bonifazzi, C., & Perri, P. (2016). The importance of glial cells in the homeostasis of the retinal microenvironment and their pivotal role in the course of diabetic retinopathy. *Life Sciences*, *162*, 54–59. https://doi.org/10.1016/j.lfs.2016.08.001

Stefan, Y., Orci, L., Malaisse-Lagae, F., Perrelet, A., Patel, Y., & Unger, R. H. (1982). Quantitation of Endocrine Cell Content in the Pancreas of Nondiabetic and Diabetic Humans. *Diabetes*, *31*(8), 694–700. https://doi.org/10.2337/diab.31.8.694

Strubbe, J., & Steffens, A. (1993). Neural Control of Insulin Secretion. *Hormone and Metabolic Research*, *25*(10), 507–512. https://doi.org/10.1055/s-2007 1002162

Summary of measurement properties of the PEDro scale. (2019, October 24). *PEDro*. https://pedro.org.au/english/summary-of-measurement-properties of-the-pedro-scale/

Sundberg, T., Leach, M., Thomson, O., Austin, P., Fryer, G., & Adams, J. (2018). Attitudes, skills and use of evidence-based practice among UK osteopaths: A national cross-sectional survey. *BMC Musculoskeletal Disorders*, *19*. https://doi.org/10.1186/s12891-018-2354-6

Suzuki, Y., Nakazawa, M., Suzuki, K., Yamazaki, H., & Miyagawa, Y. (2011). Expression profiles of cytokines and chemokines in vitreous fluid in diabetic retinopathy and central retinal vein occlusion. *Japanese Journal of Ophthalmology*, *55*(3), 256–263. https://doi.org/10.1007/s10384-011 0004-8

Swaroop, J. J., Rajarajeswari, D., & Naidu, J. N. (2012). Association of TNF-α with insulin resistance in type 2 diabetes mellitus. *The Indian Journal of Medical Research*, *135*(1), 127–130. https://doi.org/10.4103/0971 5916.93435

The pancreas in situ (Netter, F.H., Atlas of human anatomy. 6th ed. 2014,

Saunders). (2021, March 30). https://www.facebook.com/ClinAnat.OperSurg/photos/a.366852020014 40/4214604691905831/?type=3&theater
Tilg, H., & Kaser, A. (2011). Gut microbiome, obesity, and metabolic dysfunction. *The Journal of Clinical Investigation*, *121*(6), 2126–2132. https://doi.org/10.1172/JCI58109
Tokarz, V. L., MacDonald, P. E., & Klip, A. (2018). The cell biology of systemic insulin function. *Journal of Cell Biology*, *217*(7), 2273–2289. https://doi.org/10.1083/jcb.201802095
Tramontano, M., Tamburella, F., Dal Farra, F., Bergna, A., Lunghi, C., Innocenti, M., Cavera, F., Savini, F., Manzo, V., & D'Alessandro, G. (2022). International Overview of Somatic Dysfunction Assessment and
Treatment in Osteopathic Research: A Scoping Review. *Healthcare*, *10*(1), 28. https://doi.org/10.3390/healthcare10010028
Vaag, A. A. (2006). Glycemic Control and Prevention of Microvascular and Macrovascular Disease in The Steno 2 Study. *Endocrine Practice*, *12*, 89 92. https://doi.org/10.4158/EP.12.S1.89
Vijan, S., Turner, B., Williams, S., & Taichman, D. (2010). In the clinic Type 2 Diabetes. *Annals of Internal Medicine*, 16.
Vikram, V. R., Tan, S. H., Candasamy, M., & Bhattamisra, S. K. (2019). Diabetic nephropathy: An update on pathogenesis and drug development. *Diabetes & Metabolic Syndrome*, *13*(1), 754–762. https://doi.org/10.1016/j.dsx.2018.11.054
Wang, W., & Lo, A. C. Y. (2018). Diabetic Retinopathy: Pathophysiology and Treatments. *International Journal of Molecular Sciences*.
Watson, R. T., & Pessin, J. E. (2001). Intracellular Organization of Insulin Signaling and GLUT4 Translocation. *Recent Progress in Hormone Research*, *56*(1), 175–194. https://doi.org/10.1210/rp.56.1.175
Weir, G. C., & Bonner-Weir, S. (1990). Islets of Langerhans: The puzzle of intraislet interactions and their relevance to diabetes. *Journal of Clinical Investigation*, *85*(4), 983–987. https://doi.org/10.1172/JCI114574
Woldeamlak, B., & Biadgo, K. Y. and B. (2019). Role of Gut Microbiota in Type 2 Diabetes Mellitus and Its Complications: Novel Insights and Potential Intervention Strategies. *The Korean Journal of Gastroenterology*, *74*(6), 314–320. https://doi.org/10.4166/kjg.2019.74.6.314
Woodburse, R. T., & Olsen, L. L. (1951). The arteries of the pancreas. *Departments of Anatomy and Surgery, University of Michigan Medical School*, 255–270.
World Health Organization. (1999). *Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Provisional report of a WHO Consultation—Alberti—1998—Diabetic Medicine—Wiley Online Library*. https://onlinelibrary.wiley.com/doi/abs/10.1002/(SICI)1096 9136(199807)15:7%3C539::AID-DIA668%3E3.0.CO;2-S

Yamato, T. P., Maher, C., Koes, B., & Moseley, A. (2017). The PEDro scale had acceptably high convergent validity, construct validity, and interrater reliability in evaluating methodological quality of pharmaceutical trials. *Journal of Clinical Epidemiology*, *86*, 176–181. https://doi.org/10.1016/j.jclinepi.2017.03.002

Zhang, N., & He, Q.-S. (2015). Commensal Microbiome Promotes Resistance to Local and Systemic Infections. *Chinese Medical Journal*, *128*(16), 2250 2255. https://doi.org/10.4103/0366-6999.162502