Newly diagnosed diabetes - treatment plan and goals

Al-Jabiri, Abdelkarim

UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE

Abdelkarim Al-Jabiri

Newly diagnosed diabetes - treatment plan and goals

Graduate thesis

Zagreb, 2018.

This graduate thesis was made at the Department of endocrinology, KBC Zagreb, mentored by prof. dr. sc. Ivana Pavlić-Renar and was submitted for evaluation in the academic year of 2017/2018.

Abbreviations

ADA- American Diabetes Association

BG- blood glucose level

DKA- diabetic ketoacidosis

DM- diabetes mellitus

GAD- glutamic acid decarboxylase

HCV- hepatitis c virus

HNF- hepatocyte nuclear factor

IA- islet antigen

ICA- islet- cell antibodies

IDF- International Diabetes Federation

LADA- latent autoimmune diabetes of adulthood

MODY- maturity onset diabetes of the young

OGTT- oral glucose tolerance test

pH- potential of hydrogen

WHO – world health organization

Table of Contents

SUMMARY
SAŽETAK
1. Introduction 1
2. Classification 2
3. Diabetes mellitus type 1 3
3.1 Signs and symptoms 4
3.2 Aetiology 4
3.3 Epidemiology 6
3.4 Pathophysiology 7
3.5 Diagnosis 8
3.6 Treatment plans and goals 9
3.7 Clinical case examples 11
4. Diabetes mellitus type 2 12
4.1 Signs and symptoms 12
4.2 Aetiology 13
4.3 Epidemiology 14
4.4 Pathophysiology 15
4.5 Diagnosis 15
4.6 Treatment plans and goals 16
4.7 Clinical case examples 17
5. Other rare types 18
5.1 MODY 18
5.1.1 Clinical case example 19
5.2 LADA 19
5.2.1 Clinical case example 20
6. Conclusion 20
7. References 22
8. Acknowledgments 28
9. Biography 29

SUMMARY

Title: Newly diagnosed diabetes - treatment plan and goals

Author: Abdelkarim Al-Jabiri

Diabetes mellitus is a chronic disease in which the people who suffer from it are forced to change the whole dynamic of their lives. It has epidemic proportions and there is virtually no country that is not struggling against rising numbers of diabetes cases.

This thesis is a short review on the topic of "Newly diagnosed diabetes- treatment plan and goals". It covers the general overview on diabetes mellitus types. Covering signs and symptoms, aetiology, epidemiology, pathophysiology, diagnosis and treatment plan and goals of the main two types of diabetes.

Diabetes type 2 represents about 90% of diabetes cases, diabetes type 1 represents about 5% and other rare types represent the rest. The current most common treatment options and further management goals for DM type 2 are lifestyle modifications followed with non-insulin hypoglycaemic agents later requiring subcutaneous insulin injections. In DM type 1 the mainstay of treatment is subcutaneous insulin injections and further management is highly dependent on education of patients to have satisfactory control of BGs to reduce the risk of long term complications.

WHO gives the criteria on how to diagnose and differentiate diabetes types which helps clinicians worldwide to accurately diagnose diabetes. At the end a short presentation of some less known types of diabetes that still need more attention and more research.

Key words: diabetes mellitus, types, diagnosis, treatment.

SAŽETAK

Naslov: Novo dijagnosticirana šećerna bolest – plan i ciljevi liječenja

Autor: Abdelkarim Al-Jabiri

Šećerna bolest je kronična bolest u kojoj su ljudi koji pate od nje prisiljeni promijeniti cijelu dinamiku svog života. Ima razmjere epidemije i praktički nema zemlje koja se ne bori protiv povećanja broja slučajeva dijabetesa.

Ovaj diplomski rad je kratki pregledni rad na temu "Novo dijagnosticirana šećerna bolest – plan i ciljevi liječenja". Ovaj rad pokriva generalni pregled raznih tipova diabetesa mellitusa. Pokriveni su znaci i simptomi, etiologija, epidemiologija, patofiziologija, dijagnoza te plan i ciljevi liječenja dva glavna tipa dijabetesa.

Dijabetes tipa 2 predstavlja oko 90% slučajeva dijabetesa, dijabetes tipa 1 predstavlja oko 5%, a ostali rijetki tipovi predstavljaju ostatak. Sadašnje najčešće opcije liječenja i daljnji ciljevi upravljanja za DM tip 2 su promjene načina života, a potom ne- inzulinski hipoglikemijski lijekovi koji kasnije traže subkutane injekcije inzulina. U DM tip 1 glavno je liječenje subkutanim injekcijama inzulina, a daljnje upravljanje visoko ovisi o obrazovanju pacijenata da imaju zadovoljavajuću kontrolu BG-ova kako bi se smanjio rizik dugoročnih komplikacija.

WHO daje kriterije o dijagnosticiranju i razlikovanju tipova dijabetesa koji pomažu kliničarima diljem svijeta da precizno dijagnosticiraju dijabetes. Na kraju je kratko prezentirano dvoje manje poznatih tipova dijabetesa koji još trebaju više pažnje i više istraživanja.

Ključne riječi: dijabetes mellitus, tipovi, dijagnoza, liječenje

1. Introduction

Diabetes is a big health concern all over the world. Impacting not only the overall health of the population but presents as a big economic problem both through health expenditures and days of lost work. It does not concern only one specialty but requires a multidisciplinary approach. Problem of diabetes is shown not only through an increase in number of patients but also in the decreasing age at which people acquire diabetes. Diabetes is a chronic disease which affects a big part of the human population. IDF states (1) that more than 425 million people suffer from diabetes worldwide.

People with diabetes have either destruction of their pancreatic beta cells rendering them unable to produce insulin or unable to utilize the endogenous insulin created by their bodies. Insulin is a hormone in the human body produced by the pancreatic beta cells that lowers glucose in blood. Its action is opposite of glucagon produced by pancreatic alpha cells which raises blood glucose levels. Diabetes is a serious lifelong disease with serious consequences.

WHO states: “Diabetes caused 1.5 million deaths in 2012. Higher-than-optimal blood glucose caused an additional 2.2 million deaths, by increasing the risks of cardiovascular and other diseases. Forty-three percent of these 3.7 million deaths occur before the age of 70 years. The percentage of deaths attributable to high blood glucose or diabetes that occurs prior to age 70 is higher in low- and middle-income countries than in high-income countries.”(2)

Diabetes is most commonly divided into three main types. Diabetes type 1, diabetes type 2 and gestational diabetes. Diabetes has both acute and chronic consequences. Acute consequences usually entail patients using subcutaneous injections of insulin that exposes them to the risk of administering too many units of insulin and entering a hypoglycaemic state. Hypoglycaemia can lead to a diabetic coma which is a severe state where the patients lose consciousness and cannot be awakened. Prolonged state of coma and hypoglycaemia can

lead to serious glucose deficiency in the brain sometimes causing brain damage or even lead to a fatal outcome. Chronic consequences are usually caused by inadequate blood glucose level control where patients have persistent high blood sugar levels. Persistent hyperglycaemia in patients causes many organs to be at risk of many different pathologies especially microvasculature and nerves. “The prolonged hyperglycaemia leads to heart attacks, strokes, kidney failure, leg amputation, vision loss and nerve damage.”(2)

Diabetes in pregnancy or gestational diabetes has to be adequately controlled to avoid damage to the unborn foetus. The trend of acquiring diabetes is unfortunately increasing and it is not showing any signs of slowing down. Diabetes is a life long illness that doesn’t only affect people that suffer from it but the society as a whole.

2. Classification

Currently diabetes is divided into following four main divisions (3). First being diabetes type 1, second is diabetes type 2, third gestational diabetes and other specific types. Diabetes type 1 can be further subdivided into immune mediated and idiopathic types. Type 2 diabetes has no subdivisions but can range from patients unable to utilize their endogenous insulin to patients having combined inability to both produce and utilize endogenous insulin. Gestational diabetes occurs in pregnancy and may or may not disappear after the end of pregnancy. Other specific types encompass a wide range of possible pathologies. Genetic defects of beta cell function and/or insulin action. Possible pathologies of the exocrine pancreas. Endocrinopathies that adversely affect BG. Iatrogenic causes of diabetes. Monogenetic diabetes which is a consequence of a mutation of a specific gene (called MODY for historical reasons). Infections increasing the risk of acquiring diabetes. Some less common forms of immune mediated diseases may exist. Many genetic syndromes are also associated with diabetes.

In the past it was considered that there is a clear demarcation between diabetes type 1 and diabetes type 2. Diabetes type 1 was usually assumed to be a disease reserved for the paediatric population, while on the other hand diabetes type 2 was considered to be a disease affecting the older population.

As more time passed it was becoming obvious that the classification is lacking. The age boundary between the previously considered two completely different diseases with vast differences in their epidemiologic data started to blur. We see an increase in both the overall numbers of affected patients with both diseases and especially a rise in diabetes type 2 occurring more and more in the younger population of patients.

This thesis will mainly focus on type 1 and 2 diabetes, MODY (maturity onset diabetes of the young) and LADA (latent autoimmune diabetes in adults).

3. Diabetes mellitus type 1

Diabetes type 1 is a subtype of DM where patients cannot produce insulin due to destruction of beta cells of the pancreas so they need treatment with exogenous insulin. Insulin was previously extracted from cattle pancreas, but nowadays it is produced by recombinant DNA technology which enabled the creation of insulin analogues with more appropriate pharmacodynamics.

Treatment with insulin can be administered through subcutaneous injections with insulin syringes, pens or infused by pumps that have cartridges filled with insulin that is administered through cannulas that are placed likewise subcutaneously and can be used for up to two weeks.

3.1 Signs and symptoms

Polyuria (increased urination), polydipsia (increased thirst), dry mouth, polyphagia (increased hunger), fatigue, and weight loss constitute some of the most often encountered signs and symptoms in patients presenting with diabetes mellitus type 1 (2).

These signs and symptoms although obvious and usually point to a specific disease for medical professionals to the general public are quite unspecific and don't elicit much discomfort. Although the age at which any diabetes type can occur is not so obvious anymore it is still more common to present in the paediatric population so these symptoms usually get attributed to children drinking a lot of water or too many juices. For those reasons patients tend not to seek medical help until they start suffering from consequences of diabetic ketoacidosis.

Diabetic ketoacidosis is a state that the body enters because of lack of insulin that stops utilization of glucose. Additionally glucagon further raises already high blood glucose levels even further and since we lack insulin, free fatty acids get released from adipose tissues then converted via beta oxidation to ketone bodies and they start being used as energy source for the metabolism. This in turn diminishes blood pH which leads to a state of metabolic acidosis.

Signs and symptoms of diabetic ketoacidosis are the following: (4): "dry skin, rapid deep breathing, drowsiness, increased thirst, frequent urination, abdominal pain, and vomiting".

3.2 Aetiology

Although almost 100 years passed since the first use of insulin in diabetic patients and we made great improvements in management and treatment of those patients, we still don't know the exact aetiology of diabetes mellitus type 1. Many studies have been done to try and discover what is causing DM type 1.

So far we have two main animal models used in scientific literature trying to describe the processes leading to the disease, the non-obese diabetic mouse and the BioBreeding-diabetes prone rat (5). Most studies show that the aetiology must be multifactorial and that the process that leads to DM type 1 is not a simple one. Autoimmune reaction towards pancreatic beta cells leading to their destruction results in inability to control BGs.

It is postulated so far that there are many components triggering the autoimmune response such as genetic susceptibility, environmental factors and also some chemicals and drugs that have implications in DM type 1. Pociot and Lernmark (6) in their research of genetic factors involved in DM type 1 state that the primary risk factor for autoimmunity of beta cells is genetic. Patients with either HLA-DR3-DQ2 or HLA-DR4-DQ8 haplotypes, or both, seem to have an increased risk of developing DM type 1 but an environmental trigger is usually required.

Oxford handbook of endocrinology and diabetes explains us the risk of acquiring DM type 1. The lifetime risk of developing DM type 1 in the Caucasian population is below 1%. Further strengthening the claim that genes are responsible for DM type 1 is the increased risk of acquiring the disease if one of the family members is already affected by it. Risk rises to about 2% if the mother has it, while if the father has it risk is about 4% and affected siblings raise it to about 5%. Even in monozygotic twins the occurrence rate is about 50% by age 40. (7)

There are many things to take into account when talking about possible causes of DM type 1 but it seems that many do agree on the fact that environmental factors have a significant role to play in developing the disease as well as genetic factors. Knip et al. explain the following: “A series of evidence supports a critical role of exogenous factors in the development of type 1 diabetes, such as 1) the fact that <10% of individuals with HLA-conferred diabetes susceptibility do progress to clinical disease, 2) a pairwise concordance of type 1 diabetes of

<40% among monozygotic twins, 3) a more than 10-fold difference in the disease incidence among Caucasians living in Europe, 4) a several-fold increase in the incidence over the last 50 years, and 5) migration studies indicating that the disease incidence has increased in population groups who have moved from a low-incidence to a high-incidence region. (8)" Similarly, Oilinki et al. described in their research the prevalence of DM type 1 between Somali and Finish children living in Finland. They showed although the incidence of DM type 1 in Somalia is rather low, these children in the same geographical location showed similar frequency of DM type 1 maybe owing to certain environmental factors involved. (9)

Other possible causes can sometimes be more obvious in some patients. These are trauma to the pancreas, possible complications of pancreatitis, tumours and some antineoplastic agents like Streptozotocin. Streptozotocin is used in inducing DM type 1 in animal models because of its selective beta cell toxicity. Possible use is also in treatment of metastatic cancer of pancreatic islet cells that otherwise cannot be treated by surgery. (10)

3.3 Epidemiology

Talking about diabetes in general we see that it has pandemic proportions and there is basically no country that is not affected by this disease. About 5-10% of diabetes cases can be classified as DM type 1 (11).

Further supporting the idea of environmental factors being involved in aetiology of DM type 1 are national registries for newly diagnosed cases of diabetes. What these registries show like the WHO DIAMOND project is that some countries have an incidence as high as 60 cases per 100 000 annually while some have as low as 0.5 cases per 100 000 annually in children aged under 15 (2).

East Asian and Native American populations have low incidences about 0.4 cases per 100 000 annually, while the highest rates are found in Finland with more than 60 cases per 100 000

annually, Sardinia shows around 40 cases per 100 000 annually, and Sweden 47 per 100 000 annually. The risk seems to be highest in European high income countries (12). The incidence for the country of Croatia is around 8 cases per 100 000 annually (13). These differences can be further exemplified by having different genetic makeup, HLA haplotypes in different countries.

3.4 Pathophysiology

Destruction of beta cells of the pancreas is the cause of DM type 1 no matter what risk factors or triggers we consider. Autoimmune response towards the beta cells seems to be the generally accepted process by which the destruction occurs. This autoimmunity seems to be caused by autoreactive CD4+ T helper cells and CD8+ T cells, autoantibody-producing B cells and activation of the innate immune system (14).

There are researches that postulate that the causative agent or at least a trigger to the autoimmunity might be a bacteria. When talking about bacterial infections they explain that these bacteria infiltrate the pancreas through the ampulla of Vater from the gastrointestinal system. Possible causative agents are postulated to be E. Coli, Enterococcus and S. Aureus. After the initial infiltrated beta cells are destroyed the remaining beta cells seem to succumb to a big glucose load and toxicity that they need to manage which in turn leads to more beta cell destruction and ultimately to diabetes (15).

Pociot and Lernmark explain that the pathogenesis can be divided into three different stages: “1, appearance of β-cell autoimmunity, normoglycaemia, and no symptoms; 2, β-cell autoimmunity, dysglycaemia, and no symptoms; and 3, β-cell autoimmunity, dysglycaemia, and symptoms of diabetes. (6)”.

The last thing that needs explaining is the so called honeymoon period. This period occurs when the patient with DM type 1 starts the insulin treatment. After they start the treatment

they seem to have better insulin levels for a period of time. This is believed to be due to dysregulation in their immunity (16).

3.5 Diagnosis

Most common presentation of DM type 1 is polyuria (excessive urination), polydipsia (excessive thirst), and polyphagia (excessive eating or appetite). Nausea, tiredness and blurred vision also occur. All of these symptoms occur from hyperglycaemia.

When these symptoms are recognized the first pathology that comes to mind especially if coupled with a younger patient is DM type 1. To diagnose DM WHO recommends three different options for testing if the patient has the disease. Fasting plasma glucose, 2-h plasma glucose in OGTT and HbA1c.

Fasting plasma glucose is a test used by doctors to assess the concentration of glucose in blood after an 8 to 10 hour fasting period. In these 8 to 10 hours patients are instructed to not eat or drink anything except water. 2-h plasma glucose test or sometimes referred to as 2-h glucose tolerance test is performed in such a way that the patient intakes an oral dose of 75g of glucose. Dose is adjusted for adult patients below 42 kg of weight and for children. Venous blood is drawn 2 hours after ingestion to measure BG. HbA1c or glycated haemoglobin of 6.5% or more is diagnostic for DM. HbA1c value is commonly used in diabetes and can give a longer estimate of glucose levels in time over a period of three months- erythrocyte lifespan. It is necessary to have at least two positive values to diagnose DM.

Based on these tests and their results current WHO diagnostic criteria are divided into three different results (2). Impaired fasting glucose, impaired glucose tolerance and diabetes. Patient is said to have impaired fasting glucose if his fasting plasma glucose shows 6.1 to 6.9 mmol/L (110 mg/dl to 125 mg/dl) and if measured complementing this would be 2-h plasma glucose result of < 7.8 mmol/L (140 mg/dl). Impaired glucose tolerance criteria are fasting

plasma glucose of < 7.0 mmol/L (126 mg/dl) and 2-h plasma glucose of ≥ 7.8 and < 11.1 mmol/L (140 mg/dl and 200 mg/dl). Diabetes criteria are fasting plasma glucose of ≥ 7.0 mmol/L (126 mg/dl) or 2-h plasma glucose of ≥ 11.1 mmol/L (200 mg/dl) or HbA1c of ≥ 6.5% (48 mmol/mol).

3.6 Treatment plans and goals

Treatment of DM type 1 usually starts when it is discovered that the patient suffers from the disease. As previously explained usual presentation is one of polyuria, polydipsia and polyphagia. This presentation is however most common one and does not occur in every patient. The discrepancy between the usual presentation and some less common ones can affect the timing when DM type 1 is recognized. This most commonly occurs in paediatric population. Due to this delay in diagnosis many patients present with diabetic ketoacidosis.

Treatment of DKA is not simple and especially so in the younger patients. Consensus statement from ADA explains that the main points to consider in treating DKA is fluid and electrolyte replacement, insulin therapy, potassium and phosphate depletion, and acidosis (17).

Once the patient is stabilized and the risk of cerebral oedema and recurrence of DKA has lessened the patient is started on subcutaneous insulin injections. This initial point of treatment of DKA should be performed in specialized wards. During the hospital stay the education of patient parents and/or patients themselves begins. Education has to envelop as many aspects of the disease as possible to enable the patients and/or their parents to have a normal lifestyle. Although we strive to do the best we can, patients still have an enormous amount of information to process in combination with the psychological stress that they are suffering from a chronic disease that is going to affect them their whole life. Beginning of the education starts with the explanation of the disease itself. Newly diagnosed patients and their

families are naturally going to have many questions that need to be explained and elaborated to them to prepare them for their future.

Important aspect of managing diabetes is measuring the blood glucose levels. Patients need to be taught how to utilize blood glucose measuring devices to monitor their glucose. Another way of measuring glucose is with continuous glucose monitors. These monitors have glucose sensors that are placed subcutaneously and can give blood glucose measurement at any time. Although still not completely perfected more and more patients are opting for these devices since they bypass the need to have their fingers pricked on multiple occasions during the day.

Another important aspect of treatment is the actual management of glucose. First line of treatment are subcutaneous insulin injections that serve as a replacement for their endogenous insulin that they are unable to produce. Insulin can be divided into rapid, short, intermediate, and long acting types. Different types of insulin are combined to ensure the best possible glycaemic control. The long term goal is to keep the value of HbA1c below 6.5% (48 mmol/mol). Higher levels of HbA1c are tolerated in elderly patient, those with serious comorbidities, short life expectancy etc. The treatment goal regarding level of BG control is set individually (18).

The patients need to be well educated in every aspect of insulin application from administration sites and amount of insulin to be administered in accordance to the consumed food to possible side effect of overdose with insulin that leads to hypoglycaemia. Patients are given glucagon injections that are administered intramuscularly in case of hypoglycaemic coma. Other possible way of administering insulin is via insulin pumps.

These are arguably the most important parts of the patient education but one part that must not be forgotten is the lifestyle modifications that the patients has to go through. Balanced carbohydrates in the diet and exercise are necessary in DM type 1 to have best possible

results. Smoking should be avoided completely since it has heavy implication in increasing the risk of microvasculature damage that is already increased in diabetics. Alcohol should be consumed carefully and in moderation since it can make the management of a hypoglycaemic episode very difficult. Without the patient making an effort to implement these changes their glycaemic control is going to be suboptimal if not completely out of their control.

Other possible treatment options are islet cell transplant and pancreas transplant. Both are not commonly used. There are many limitations to using these methods but the most notable one is immunosuppression. Generally the clinicians will not chose these options unless really necessary.

3.7 Clinical case examples

Case 1

Male, born in 1941. Diabetes diagnosed in 2008 (67 years at the time of diagnosis). Family history is negative. Body mass stable, low. There was no symptoms of hyperglycaemia at diagnosis, HbA1c was 8.0%. After one year despite the three-drug therapy (metformin, gliclazide, pioglitazone) high glycemia, HbA1c up to 9%, for that reason it was initiated to begin with insulin in 2 doses. Glucoregulation is unstable, started basal - bolus therapy. GAD antibodies test performed- high titer.

Diagnosis- type 1 diabetes with onset occuring in the older age.

Case 2

Female, born in 1991. Hospitalized in 2016 (24 years at the time of hospitalization) with uroinfection. After a month - two instances of polydipsia, weight loss (8 kg). At the time hyperglycemia (29 mmol / L) without acidosis. Started basal- bolus therapy but after 2 months interrupted after reducing insulin dose due to frequent hypoglycemia. ICA and GAD positive.

During 2018, due to the worsening of glucose regulation, insulin is gradually introduced, first with the bolus therapy.

Diagnosis- type 1 diabetes with the honeymoon period.

Case 3

Male, born in 1976. Diabetes since 2017, due to high glycemic levels immediately initiated insulin treatment.

From anamnesis: Alcoholism and anxiety syndrome from the mid-2000s. He was treated as a psychiatric patient, now he does not drink. On three occasions had acute pancreatitis episodes 2014 - 2016.

Diagnosis- ”*other”* diabetes (pancreatic).

4. Diabetes mellitus type 2

Diabetes type 2 is a subtype of DM that is usually seen as high BG, insulin resistance and sometimes insulin deficiency. Lifestyle and an increasing trend of more and more people becoming obese might be the main culprits behind the pandemic that is DM type 2.

4.1 Signs and symptoms

Signs and symptoms of DM type 2 are quite similar to DM type 1 signs and symptoms. The notable difference is in how the disease is usually recognized. DM type 1 inadvertently leads to excessive and obvious symptomatology that usually hospitalizes the patient before it is discovered while DM type 2 most commonly has a more insidious onset and takes some time before being discovered.

This can be attributed to the fact that most patients have only a partial initial insulin resistance at least at the beginning of the pathology and not a complete one. Same can be said for the lack of insulin production, patient that is in the developing phase of the disease doesn't necessarily have to have damage to the endocrine pancreas. For these reasons usual time and place of discovery of the DM type 2 happens in the setting of systematic check-ups. Usual presentation again attributable to hyperglycaemia is of polyuria, polydipsia, polyphagia and weight loss (19). Other symptoms can include but are not limited to dry mouth, fatigue, blurred vision, decreased vision, headaches, difficult to heal trauma, itchy skin, recurrent yeast infections, paraesthesia of hands and feet, etc. It is important to be aware of these symptoms to be able to discover the disease as early as possible.

The sooner the treatment is implemented the better, since the risk of complications decreases due to decreased amount of time that the patient's body has their homeostasis disrupted.

4.2 Aetiology

Development of DM type 2 cannot be attributed to a single process. Multitude of causative factors need to be taken into account when discussing the cause of this pathology. Main culprits behind the process are lifestyle habits, genetics and iatrogenic causes. Interestingly even lack of sleep has been attributed to the development of DM type 2 due to its adverse effects on the body (20).

WHO also explains additional risks that may lead to DM type 2: "Ethnicity, family history of diabetes, and previous gestational diabetes combine with older age, overweight and obesity, unhealthy diet, physical inactivity and smoking to increase risk. (2)"

Lifestyle factors such as sedentary lifestyle, obesity and being overweight, lack of physical activity, poor diet, stress, and urbanization all have an active role to play in the aetiology (21). Regarding genes involved in the development of DM type 2, we have accounted for 36 genes

which in turn translates to about 10% of the total heritable component of the disease (22). Iatrogenic causes include glucocorticoids, thiazides, beta blockers, atypical antipsychotics, etc. (23).

Although genes and iatrogenic causes cannot be avoided the part that can be influenced the most is definitely lifestyle. However, it is more "inheritable" than type 1 – concordance in monozygotic twins is 90% or more (24). If the habits of physical exercise and a properly regulated diet are implemented early enough in life it can reduce the risk of not only DM type 2 but many other diseases. For these reasons the importance of the public health sector becomes apparent both for the clinicians and the population.

4.3 Epidemiology

In 2015 T. Vos, C. Allen, M. Arora, et al. estimated that there were 392 million people with type 2 diabetes making up about 90% of diabetes cases which means that about 6% of the human population suffers from this disease (25).

DM type 2 in 1985 was estimated at 30 million, 135 million in 1995 and 217 million in 2005 (26). Because of population aging and a sedentary lifestyle leading to increasing rates of obesity we see increased rates of this disease (26).

Certain ethnic groups like South Asians, Pacific Islanders, Latinos, and Native Americans seem to be at an increased risk (19). Countries with the greatest number of people with diabetes as stated in "Global prevalence of diabetes: estimates for the year 2000 and projections for 2030" are India having 31.7 million, China 20.8 million, the United States 17.7 million, Indonesia 8.4 million, and Japan 6.8 million (27). This data shows us how much of a burden this particular disease is in the world and that it has pandemic proportions.

4.4 Pathophysiology

While discussing the pathophysiology of DM type 2 we need to include insulin resistance and insulin secretion deficiency. This would be satisfactory to explain the main ideas behind the processes that lead to DM type 2. To get an even better understanding of the concept we also need to include the explanation of the feedback loop between the beta cells of the pancreas and the insulin sensitive tissues.

Communication between the beta cells and the insulin sensitive tissues occurs through mediators that are yet to be determined. Insulin is responsible for enabling the uptake of glucose, amino acids and fatty acids into insulin-sensitive tissues while tissues respond letting the beta cells know how much insulin they need. For that reason in the setting of insulin resistance the beta cells are going to secrete more and more insulin. When the load becomes too great we see an elevation in BG. Further deterioration leads from prediabetes to frank DM type 2 (28).

Many things cause tissues to become insulin resistant. Most common reason is insulin resistance occurring in the setting of obesity, other reasons include certain molecular mechanisms, genetic factors, diet, sedentary lifestyle and HCV.

There seems to be a connection between the duodenum and insulin resistance in tissues. Some new small scale experimental research show that there might be a possible surgical intervention for non-obese related insulin resistance and DM type 2 (29), with more research we might get a new clue towards the exact reasons behind insulin resistance and development of DM type 2.

4.5 Diagnosis

The WHO criteria that are used for diagnosis of DM has been explained in section 3.5. of this thesis.

The difference that can help the clinicians in differentiating between these two pathologies is in the presenting circumstances. On one hand we have DM type 1 which presents quite soon after the onset of symptoms, on the other hand the course of DM type 2 is more insidious and takes more time to present with symptoms. DM type 2 often shows no symptoms, patients might contact their doctors because of complications or they can simply be diagnosed during routine check-ups (2). One potentially useful laboratory test in differentiating DM type 1 and 2 is C-peptide levels. C-peptide levels, especially after a meal are low in type 1 diabetes and normal or high in type 2 diabetes (30).

The key in better management of DM type 2 is early diagnosis. Although it is very important to discover the disease as soon as possible the question of performing or not performing screening for DM type 2 is still a heavily debated topic (2).

4.6 Treatment plans and goals

Treatment of DM type 2 encompasses lifestyle modifications, pharmacological management and surgery. While DM type 1 usually focuses on stricter BG controls the primary goal in DM type 2 management is a healthier lifestyle to control the cardiovascular risk factors. Since most patients that present with this disease have poor habits and are usually obese the idea is to educate them on how to change those habits and how to reduce weight.

Smoking cessation and exercise help in improving hypertension. Current recommendation is to keep the systolic blood pressure between 140 to 150 mmHg. Keeping the systolic blood pressure below 140 mmHg is associated with lower morbidity and mortality (31). Diets like low glycaemic index diet or low carbohydrate diet can help improve BG (32).

When discussing DM type 2 that is already an established disease that unfortunately cannot be managed purely with lifestyle modifications and pharmacological therapy needs to be instituted. First line therapy is metformin. Another class of medication or insulin may be

added if metformin is not controlling BGs acceptably after three months. Other classes include: sulfonylureas, thiazolidinedione's, dipeptidyl peptidase-4 inhibitors, SGLT2 inhibitors, and glucagon-like peptide-1 analogues (33). Angiotensin-converting enzyme inhibitors (ACEIs) help prevent kidney disease and improve outcomes in patients with diabetes (34). As a last step if oral medication is not sufficient to control BGs adding subcutaneous insulin injections help in management.

In patients that have problems with controlling BGs and are unable to lose weight bariatric surgery is a viable option for managing diabetes (35).

4.7 Clinical case examples

Case 1

Female, 55 years of age. Body mass decreasing, BMI 28. Has hypertension as a comorbidity. HbA1c 11.3%, hyperglycaemia 17.2 mmol/L and ketones of 0.1 mmol/L. DPP4 inhibitor and pioglitazone added. After 3 months body mass stable, HbA1c 6.3%.

Diagnosis- type 2 diabetes.

Case 2

Female, 55 years of age. Body mass decreasing, BMI 21. Has no comorbidity. HbA1c 12.0%, hyperglycaemia 18.5 mmol/L and ketones of 0.7 mmol/L. Gliclazide added, possible initiation of insulin considered. However, the patient came after 3 months with increased body mass and HbA1c 6.5%. GAD was tested and revealed a negative result.

Diagnosis- type 2 diabetes.

Case 3

Male, 62 years of age. Body mass decreasing, BMI 29. Has hypertension as a comorbidity and he is also a cardiology patient. HbA1c 12.0%, hyperglycaemia 20.0 mmol/L. Metformin added. After 3 months body mass decreased, HbA1c 6.3%.

Diagnosis- type 2 diabetes.

Case 4

Female, 74 years of age. Body mass stable, BMI 29. Has hypertension as a comorbidity, had a cerebrovascular insult and cardiac decompensation. HbA1c 10.9%, hyperglycaemia 27.2 mmol/L and ketones of 0.1 mmol/L. Gliklazid and metformin added. After 3 months body mass stable, HbA1c 6.2%.

Diagnosis- type 2 diabetes.

5. Other rare types

5.1 MODY

Maturity onset diabetes of the young is one of the rare types of diabetes and has an autosomal dominant inheritance due to a mutation in one gene. Only about 1-2% of diabetes cases are attributed to MODY. Since the education of general practitioners for these less common types of diabetes is still lacking it is estimated that up to 90% percent of MODY cases are either diagnosed as DM type 1 or 2.

Some of the key features of MODY are; patients are diagnosed before they are 25 years of age, have a family history of diabetes for at least 2 generations and they don't necessarily require insulin treatment.

Subtypes of MODY have different gene mutations and the most common mutations are on genes: HNF1-alpha, HNF4-alpha, HNF1-beta and glucokinase (36). It is important to recognize that the patient has MODY since the treatment is going to differ in subtypes of the

disease. Being aware which subtype it is helps in advising the patients on what to expect and also to help prepare them for family planning.

5.1.1 Clinical case example

Case 1

Male, born in 1990. Diabetes from 2014 (24 years at the time of initial diagnosis). No symptoms, high glycaemia (17mmol / L) observed on a check-up for mycosis treatment, HbA1c was 9.1%. Mother and grandmother have diabetes, they do not take insulin, mother's sister takes insulin from the time of her diagnosis. Started with insulin in the basal- bolus scheme. The dose gradually decreased. ICA and GAD negative. There is suspicion for monogenetic diabetes. HNF4- alpha positive. Started with a low dose of gliclazide, HbA1c is 6.5%.

Diagnosis- MODY 1

5.2 LADA

Latent autoimmune diabetes in adults is a form of DM type 1 that develops later in life. Prof. David Leslie, defines LADA as: “initially non-insulin requiring diabetes diagnosed in people aged 30-50 years with antibodies to GAD - glutamic acid decarboxylase” (37).

Once more the problem of insufficient education is one of the culprits behind the fact that most cases of LADA are misdiagnosed as DM type 2. Symptoms of LADA are quite similar to DM type 2 and thus lead to the wrong diagnosis. With progression of the disease deficiency of insulin becomes more pronounced and starts exhibiting similar symptoms to DM type 1.

A study done in the UK found that antibodies specific to LADA cases are found in about 8% of DM cases (37). With lifestyle modification it is possible to postpone the need for insulin treatment but the treatment itself is inevitable.

5.2.1 Clinical case example

Case 1

Male, born in 1981. Diabetes discovered in 2007 (26 years at the time of diagnosis). Father has type 2 diabetes. BMI at the time of diagnosis was 25, body mass stable. There were no symptoms, HbA1c was 7.0%. GAD and IA2 positive. Received insulin once, but with diet and metformin achieved the ideal glucoregulation, HbA1c about 6% by 2013. Gained weight (BMI up to 31). Because of the worsening of glucose regulation, basal insulin (detemir) with DPP4 (sitagliptin) and metformin added in 2013. Wasn't adhering to therapy, last control in 2015 after a prolonged period of time – stoped taking insulin, metformin taken regularly, body mass too high (BMI 30), HbA1c 6.5%.

Diagnosis- LADA.

6. Conclusion

Diabetes is a special challenge for patients, their families, clinicians, public health workers and the society as a whole. For many years now a lot of effort has been put into researching all aspects of the disease from its aetiology to the optimal treatment methods for all types of diabetes. Although we still don't have the complete picture of every aspect of diabetes we made great strides forward in improving both morbidity and mortality of diabetes patients. The life expectancy for diabetic patients is coming closer and closer to that of the healthy population.

Probably the most important idea that needs elaboration is that diabetes treatment is not necessarily a rigid, inflexible set of rules and needs to be tailored to the individual and not the disease. An appropriate example of that would be that in DM type 1 patients the most common basal- bolus scheme for insulin is 50-50% but in some cases such a scheme could be

counterproductive. If the patient has a lifestyle where he or she eat multiple times a day and possibly see that they have better glucose control on a basal- bolus scheme of 40-60% they should be able and allowed to do so, to accommodate the disease to their lifestyle and not the other way around. Likewise, in any other type of diabetes if the patient is not in complete accordance to the guidelines but they have good glucose regulation and their HbA1c levels are satisfactory they should be enabled and feel that they can ask for advice on their actions from the physicians.

In conclusion, we should strive for improvement in every aspect of the disease and hopefully as the end goal we will be able to not only improve patient's lives but to cure diabetes.

7. References

1. Interantional Diabetes Federation. Idf Diabetes Atlas [Internet]. 8th ed. 2017. Available from: http://www.diabetesatlas.org/

2. World Health Organization. Global Report on Diabetes. Isbn [Internet]. 2016;978:88. Available from: http://www.who.int/about/licensing/%5Cnhttp://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf

3. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care [Internet]. 2014 Jan 1;37(Supplement_1):S81–90. Available from: http://care.diabetesjournals.org/cgi/doi/10.2337/dc14-S081

4. WebMD. Type 1 Diabetes-Symptoms [Internet]. 2018 [cited 2018 May 2]. Available from: https://www.webmd.com/diabetes/type-1-diabetes-guide/type-1-diabetes-symptoms#1

5. Roep BO, Atkinson M, von Herrath M. Opinion: Satisfaction (not) guaranteed: re-evaluating the use of animal models of type 1 diabetes. Nat Rev Immunol [Internet]. 2004 Dec;4(12):989–97. Available from: http://www.nature.com/doifinder/10.1038/nri1502

6. Pociot F, Lernmark Å. Genetic risk factors for type 1 diabetes. Lancet [Internet]. 2016 Jun;387(10035):2331–9. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0140673616305827

7. Wass J, Turner H, Owen K, editors. Oxford Handbook of Endocrinology and Diabetes. In: Oxford Handbook of Endocrinology and Diabetes. Third edit. Oxford University Press; 2014. p. 690.

8. Knip M, Veijola R, Virtanen SM, Hyoty H, Vaarala O, Akerblom HK. Environmental Triggers and Determinants of Type 1 Diabetes. Diabetes [Internet]. 2005 Dec 1;54(Supplement 2):S125–36. Available from: http://diabetes.diabetesjournals.org/cgi/doi/10.2337/diabetes.54.suppl_2.S125

9. Oilinki T, Otonkoski T, Ilonen J, Knip M, Miettinen P. Prevalence and characteristics of diabetes among Somali children and adolescents living in Helsinki, Finland. Pediatr Diabetes [Internet]. 2012 Mar;13(2):176–80. Available from: http://doi.wiley.com/10.1111/j.1399-5448.2011.00783.x

10. Brentjens R, Saltz L. ISLET CELL TUMORS OF THE PANCREAS. Surg Clin North Am [Internet]. 2001 Jun;81(3):527–42. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0039610905701419

11. Daneman D. Type 1 diabetes. Lancet [Internet]. 2006 Mar;367(9513):847–58. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0140673606683414

12. Tuomilehto J. The Emerging Global Epidemic of Type 1 Diabetes. Curr Diab Rep [Internet]. 2013 Dec 27;13(6):795–804. Available from: http://link.springer.com/10.1007/s11892-013-0433-5

13. Stipancic G, La Grasta Sabolic L, Malenica M, Radica A, Skrabic V, Tiljak MK. Incidence and trends of childhood Type 1 diabetes in Croatia from 1995 to 2003. Diabetes Res Clin Pract [Internet]. 2008 Apr;80(1):122–7. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0168822707005311

14. Chatzigeorgiou A, Harokopos V, Mylona-Karagianni C, Tsouvalas E, Aidinis V, Kamper E. The pattern of inflammatory/anti-inflammatory cytokines and chemokines in type 1 diabetic patients over time. Ann Med [Internet]. 2010 Sep 23;42(6):426–38. Available from: http://www.tandfonline.com/doi/full/10.3109/07853890.2010.495951

15. Korsgren S, Molin Y, Salmela K, Lundgren T, Melhus Å, Korsgren O. On the Etiology of Type 1 Diabetes. Am J Pathol [Internet]. 2012 Nov;181(5):1735–48. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0002944012005901

16. Aly H, Gottlieb P. The honeymoon phase: intersection of metabolism and immunology. Curr Opin Endocrinol Diabetes Obes [Internet]. 2009 Aug;16(4):286–92. Available from: https://insights.ovid.com/crossref?an=01266029-200908000-00003

17. Wolfsdorf J, Glaser N, Sperling MA. Diabetic Ketoacidosis in Infants, Children, and Adolescents: A consensus statement from the American Diabetes Association. Diabetes Care [Internet]. 2006 May 1;29(5):1150–9. Available from: http://care.diabetesjournals.org/cgi/doi/10.2337/dc06-9909

18. American Diabetes Association. 6. Glycemic Targets: Standards of Medical Care in Diabetes—2018. Diabetes Care [Internet]. 2018 Jan;41(Supplement 1):S55–64. Available from: http://care.diabetesjournals.org/lookup/doi/10.2337/dc18-S006

19. Vijan S. Type 2 Diabetes. Ann Intern Med [Internet]. 2010 Mar 2;152(5):ITC3-1. Available from: http://annals.org/article.aspx?doi=10.7326/0003-4819-152-5-201003020-01003

20. TOUMA C, PANNAIN S. Does lack of sleep cause diabetes? Cleve Clin J Med [Internet]. 2011 Aug 1;78(8):549–58. Available from: https://www.mdedge.com/ccjm/article/95530/diabetes/does-lack-sleep-cause-diabetes

21. Abdullah A, Peeters A, de Courten M, Stoelwinder J. The magnitude of association between overweight and obesity and the risk of diabetes: A meta-analysis of prospective cohort studies. Diabetes Res Clin Pract [Internet]. 2010 Sep;89(3):309–19. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0168822710001944

22. Herder C, Roden M. Genetics of type 2 diabetes: pathophysiologic and clinical relevance. Eur J Clin Invest [Internet]. 2011 Jun;41(6):679–92. Available from: http://doi.wiley.com/10.1111/j.1365-2362.2010.02454.x

23. Izzedine H, Launay-Vacher V, Deybach C, Bourry E, Barrou B, Deray G. Drug-induced diabetes mellitus. Expert Opin Drug Saf [Internet]. 2005 Nov 28;4(6):1097–109. Available from: http://www.tandfonline.com/doi/full/10.1517/14740338.4.6.1097

24. Medici F, Hawa M, Ianari A, Pyke DA, Leslie RDG. Concordance rate for Type II diabetes mellitus in monozygotic twins: actuarial analysis. Diabetologia [Internet]. 1999 Jan 21;42(2):146–50. Available from: http://link.springer.com/10.1007/s001250051132

25. Vos T, Allen C, Arora M, Barber RM, Bhutta ZA, Brown A, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet [Internet]. 2016 Oct;388(10053):1545–602. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0140673616316786

26. Smyth S, Heron A. Diabetes and obesity: the twin epidemics. Nat Med [Internet]. 2006 Jan 1;12(1):75–80. Available from: http://www.nature.com/articles/nm0106-75

27. Wild S, Roglic G, Green A, Sicree R, King H. Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care [Internet]. 2004 May 1;27(5):1047–53. Available from: http://care.diabetesjournals.org/cgi/doi/10.2337/diacare.27.5.1047

28. Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. Lancet [Internet]. 2014 Mar;383(9922):1068–83. Available from:

http://linkinghub.elsevier.com/retrieve/pii/S0140673613621546

29. Goodman A. Duodenal resurfacing achieves metabolic benefits in type 2 diabetes | Family Practice News [Internet]. 2016 [cited 2018 May 21]. Available from: https://www.mdedge.com/familypracticenews/article/109286/gastroenterology/duodenal-resurfacing-achieves-metabolic-benefits

30. Leighton E, Sainsbury CA, Jones GC. A Practical Review of C-Peptide Testing in Diabetes. Diabetes Ther [Internet]. 2017 Jun 8;8(3):475–87. Available from: http://link.springer.com/10.1007/s13300-017-0265-4

31. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood Pressure Lowering in Type 2 Diabetes. JAMA [Internet]. 2015 Feb 10;313(6):603. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2014.18574

32. Thomas D, Elliott EJ. Low glycaemic index, or low glycaemic load, diets for diabetes mellitus. Cochrane Database Syst Rev [Internet]. 2009 Jan 21; Available from: http://doi.wiley.com/10.1002/14651858.CD006296.pub2

33. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia [Internet]. 2015 Mar 13;58(3):429–42. Available from: http://link.springer.com/10.1007/s00125-014-3460-0

34. Lv J, Perkovic V, Foote C V, Craig ME, Craig JC, Strippoli GF. Antihypertensive agents for preventing diabetic kidney disease. Cochrane Database Syst Rev [Internet]. 2012 Dec 12; Available from: http://doi.wiley.com/10.1002/14651858.CD004136.pub3

35. Picot J, Jones J, Colquitt J, Gospodarevskaya E, Loveman E, Baxter L, et al. The

clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: a systematic review and economic evaluation. Health Technol Assess (Rockv) [Internet]. 2009 Sep;13(41). Available from: https://www.journalslibrary.nihr.ac.uk/hta/hta13410/

36. Diabetes UK. Maturity onset diabetes of the young (MODY) - Diabetes UK [Internet]. 2017 [cited 2018 May 24]. Available from: https://www.diabetes.org.uk/diabetes-the-basics/other-types-of-diabetes/mody

37. Diabetes.co.uk. Diabetes LADA [Internet]. 2017 [cited 2018 May 24]. Available from: https://www.diabetes.co.uk/diabetes_lada.html

8. Acknowledgments

I would like to express my gratitude to my mentor prof. dr. sc. Ivana Pavlić-Renar for having the patience to guide me through this thesis from the beginning to the end. A sincere thank you to all my family, friends and colleagues for supporting me through all these years.

9. Biography

Abdelkarim Al-Jabiri, born on the 12.08.1994. in Zagreb, Croatia. Graduated from University of Zagreb, School of Medicine in the year of 2018. During his medical studies he accumulated many different experiences. Ranging from field work, during the refugee crisis in 2016, where he volunteered as a translator and a fourth year medical student in the medical tent that was acting on the border of Croatia and Slovenia all the way to practical skills in different hospitals in Zagreb. In the future he hopes to help people not only deal with their diseases but also to teach them in leading healthier and better lives.