Thesis

The impact of COVID-19 on the management of type 2 diabetes

-A pandemic within a pandemic

submitted by

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Graz, January 28th, 2023

Declaration of Academic Integrity

I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Graz, January 28th, 2023 *Marlene Kienast m.p*

Acknowledgement

Now that I have been working on this thesis for several months I would like to say thank you. First and foremost I would like to express my gratitude to Ao.Univ.-Prof.^{in} Dr.^{in} phil. Dr.^{in} h.c. Irmgard Lippe, who kept supporting me with expert advice, inventiveness in planning and writing since the very beginning of this thesis.

My further thanks go to my family who continuously motivated me to not postpone the writing of this thesis any longer, but finally complete it. A person without whom I wouldn’t have been able to conclude this academic piece of writing satisfactorily is my brother. With his excellent English skills and professional expertise he was the most perfect involuntarily chosen proof reader.

At last, I would also like to thank my fellow students and my friends from other disciplines, who gave me additional encouragement in discussions and also passed on valuable and helpful tricks and tips for writing a thesis.

Table of Contents

List of Abbreviations

A. D.	Anno Domini
ACCORD	Action to Control Cardiovascular Risk in Type 2 Diabetes
ACE2	angiotensin-converting enzyme 2
ADVANCE	Action in Diabetes and Vascular Disease-PreterAx and DiamicroN Controlled Evaluation
AGEs	advanced glycation end products
ALT	Alanine aminotransferase
AMPK	Adenosine monophosphate-activated protein kinase
ARDS	acute respiratory distress syndrome
ATP	adenosine triphosphate
BC	Before Christ
BMI	Body Mass Index
COVID-19	Coronavirus Disease 2019
CRP	C-reactive protein
DPP-4 inhibitors	Dipeptidyl peptidase-4 inhibitor
eNOS	endothelial Nitric Oxide Synthase
GIP	Glucose-dependent insulinotropic peptide
GLP1 RA	Glucagon-like peptide-1 receptor agonists
GLP-1	Glucagon-like peptide 1
GLUT-4	glucose transporter type 4
HbA_{1c}	glycosylated haemoglobin A_{1c}

HDL	high-density lipoprotein
i.e.	id est (that is)
ICU	intensive care unit
IDF	International Diabetes Federation
IL-18	interleukin-18
IL-6	interleukin-6
LDL	low-density lipoprotein
MCP-1	monocyte chemoattractant protein-1
NO	Nitric oxide
NO2-	nitrite
NO3-	nitrate
Nt-pro-BNP	N-terminal prohormone of brain natriuretic peptide
NYHA	New York Heart Association
PDX1	pancreatic and duodenal homeobox 1
PPAR-gamma	peroxisome proliferator-activated receptor gamma
PREDIMED	PREvención con DIeta MEDiterránea
RAAS	renin–angiotensin–aldosterone system
ROS	reactive oxygen species
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCFAs	short-chain fatty acids
SGLT2 inhibitors	Sodium-glucose transport protein 2 inhibitors
SUR-1	sulfonylurea receptor-1
T2DM	type 2 diabetes mellitus

TNFα	tumor necrosis factor alpha
UK	United Kingdom
USA	United States of America
WHO	World Health Organisation

List of figures

List of tables

Abstract in German

Mit rund 537 Millionen betroffenen Menschen weltweit (International Diabetes Federation 2021) gehört die endokrinologische Erkrankung Diabetes mellitus neben Hormonmangelzuständen sowie der Adipositas definitiv zu den häufigsten. Zu 90% handelt es sich bei den PatientInnen um einen Typ 2 Diabetes mellitus. Die Zahlen steigen stetig, so spielen auch die Lockdowns bedingt durch die jüngste Covid-Pandemie eine wesentliche Rolle in der Abnahme der körperlichen Aktivität und einer oftmals damit einhergehenden Gewichtszunahme.

Die dadurch entstehenden Auswirkungen auf die Gesellschaft liegen klar auf der Hand: Neben Unmengen an Kosten für das Gesundheitssystem ergibt sich durch diese Erkrankung für die DiabetikerInnen auch eine enorme soziale Belastung.

Umso wichtiger sind Präventionsvorkehrungen, sowie eine entsprechende Forcierung einer möglichst frühzeitigen Krankheitserkennung in Form von Screeningmethoden, wie beispielsweise der Bestimmung des HbA_{1c} -Wertes eines Risikokollektivs.

Einen wesentlichen Teil zur Eindämmung dieser bereits vor der „COVID-Krise“ vorherrschenden Pandemie leistet neben konservativen Therapiemethoden vor allem die Pharmakologie. Da diese Erkrankung auch nahezu sämtliche Ethnien und Bevölkerungsgruppen der Welt betrifft, stellt die Suche nach pharmakologischen Interventionsmöglichkeiten zu Recht einen allumfassenden Gegenstand der globalen Forschung dar. Die Reduktion von Folgeerscheinungen einer Hyperglykämie, der Mortalität, sowie der Morbidität sind entscheidende Ziele.

Als zentraler pharmakologischer Therapiepfeiler eines Typ 2 Diabetes mellitus sind die oralen Antidiabetika, allen voran das Biguanid Metformin, an erster Stelle zu nennen. Auch neuere Substanzgruppen, wie die SGLT2-Inhibitoren oder die subcutan verabreichbaren GLP1- Rezeptoragonisten, haben in den letzten Jahren zunehmend an Bedeutung gewonnen. Vor allem im Zusammenhang mit kardialen RisikopatientInnen bieten diese neueren Medikamentengruppen eine sinnvolle Kombinationstherapie mit dem herkömmlichen Metformin.

Auch im Rahmen der Infektionskrankheit COVID-19, welche bei vorgeschädigten Zuckerkranken eine nachgewiesene höhere Mortalität mit sich bringt, gibt es Überlegungen bezüglich einer adaptierten Therapie mit Antidiabetika, welche das Outcome in gegebenem Zusammenhang potenziell verbessern könnte.

Mit dieser relativ jungen, noch unerforschten Thematik befassen sich nicht nur die aktuelle Forschung, sondern auch daraus abgeleitete Studien.

Fakt ist, dass der Typ 2 Diabetes mellitus und die damit einhergehenden Folgen gravierende Probleme für die weltweite Bevölkerung darstellen. Deshalb ist die Eruierung weiterer Therapieoptionen, beispielsweise neue Kombinationen verschiedener Substanzgruppen, von größtem Wert für die Wissenschaft, als auch die Klinik sind.

Abstract in English

With around 537 million people affected worldwide (International Diabetes Federation 2021) the endocrinological disease diabetes mellitus along with hormone deficiencies and obesity is one of the most common. 90% of patients with diabetes suffer from type 2.

The resulting impact on society is clear: in addition to enormous costs for the health care system this disease also results in a huge social burden for diabetics.

This makes it even more important to take preventive measures and to push for the earliest possible detection of the disease in the form of screening methods, such as determining the HbA_{1c} level of a population at risk.

In addition to conservative treatment methods, pharmacology in particular is playing a key role in containing this pandemic, which was already prevalent before the "COVID crisis". Since this disease also affects almost all ethnicities and populations of the world, the search for pharmacological intervention options rightly represents an all-encompassing subject of global research. Reductions of sequelae of hyperglycemia, mortality as well as morbidity are critical goals.

As the central pharmacological pillar of therapy for type 2 diabetes mellitus, the oral antidiabetic drugs, first and foremost the biguanide metformin, must be mentioned. Newer substance groups, such as the SGLT2 inhibitors or the GLP1 receptor agonists, have also become increasingly important in recent years. Especially in the context of cardiac risk patients these newer drug groups offer a useful combination therapy with the conventional metformin.

In the context of the infectious disease COVID-19, which has been shown to increase mortality in pre-diabetic patients, there are considerations for an adapted therapy with antidiabetic drugs, which could potentially improve the outcome in the given context.

This relatively new and unexplored topic is not only addressed by current research, but also by derived studies.

It is a fact, that type 2 diabetes mellitus and its consequences represent serious problems for the worldwide population. Therefore, exploration of further therapy options, for example new combinations of different substance groups, is of utmost value for science as well as clinic practice.

1 Introduction

1.1 A brief history on the discovery of diabetes mellitus

Excessive thirst, polyuria, fatigue, wound healing disorders - these are just some of the symptoms with which one of the most common diseases of our time presents itself: Type 2 diabetes mellitus.

Records of this disease can be found as far back as several thousand years before Christ. The first documented case goes back to the ancient Egyptians and is dated 1500 BC. This so-called "Ebers Papyrus" already described the typical symptoms of diabetes mellitus at that time. Nevertheless, the basic anatomical background knowledge was lacking to even begin identifying the pathomechanism and the disease background. (1)

A first step towards understanding diabetes mellitus was taken by Sushruta, an Indian surgeon in the fifth century BC. He described the honey-sweet tasting urine which to this day still gives the disease its name. Even back then, he already noted an above-average incidence of the observed phenomenon among the rich and well-fed of society.

In other parts of the world, such as China, early records from the seventh century A.D. have also been mentioning a disease with excessively high thirst, resulting in abnormal drinking behaviour, and a large amount of urine. (1)

Aretaios of Cappadocia, a Greek physician alive in the second century A.D., first used the term "diabaino," a Greek verb that loosely translates as "to flow through," to describe this phenomenon. (2)

This polyuria was finally decisive for the modified name of diabetes, which is still valid today.

In the 17th century, the English physician Thomas Willis was also concerned with the conspicuously sweet-smelling urine. He was the first European to compare this taste and smell with honey, which he subsequently wrote down in his research using the Latin term "mellitus". He also already associated the condition with an unhealthy diet, excessive consumption of alcoholic beverages, and an often accompanying impaired psychological state of those affected. Nevertheless, the exact mechanism of origin of the disease and its symptoms remained a mystery to him. (3)

Another groundbreaking discovery in the study of the etiopathogenesis of diabetes mellitus was provided by an experiment conducted in 1889 by Oskar Minkowski and Joseph von Mering. Removal of the pancreas from dogs confirmed the organs endocrine function in sugar metabolism, which had previously only been suspected. After pancreatectomies in several dogs, the characteristic glucose-containing urine could be detected in polyuria. Interesting is also the reverse experimental approach of Minkowski quasi as a control of the found connection: after a reimplantation of a small portion of pancreatic tissue into the same experimental animals he gained the knowledge that this implant prevented the hyperglycaemia that had occurred. (1)

These experiments and the knowledge gained from them now in turn provided starting points for further research.

The exact mechanism behind the blood sugar controlling function of the pancreas was still enigmatic. It was not until 1921 that the Canadian surgeon Frederick Banting and the University of Toronto professor John Macleod, together with the medical student Charles Best devoted themselves to further decisive experiments in this field. In the institute laboratory provided, they finally tested Banting's hypothesis, according to which ligation of the pancreatic ducts prior to pancreatectomy led to destruction of the exocrine part, but not of the endocrine-acting secretion produced in the islets of Langerhans.

This substance, which was purely hypothetical at the time, was given the term "insulin" as early as 1909. However, its existence and effect had not yet been directly proven. The Nobel Prize winning proof was finally achieved using dogs made diabetic by pancreas removal on the one hand and dogs with surgically strangulated pancreatic duct on the other. Despite the ligation, the islets of Langerhans continued to produce insulin, which, as we know now is stored in vesicles in the pancreas itself. These modified organs were removed after ten weeks, crushed with a mortar and mixed with physiological saline so that an infusion of this mixture could be made. And indeed: after intravenous application in the pancreasless, diabetic dogs, there was a significant drop in hyperglycaemic blood glucose levels two hours later. To verify this discovery, the researchers repeated their experiment in calves. (4,5)

This ray of hope for the treatment of diabetes mellitus requiring insulin was finally tested and confirmed by direct application tests on humans.

Initially the unpurified insulin obtained from animals at that time led to many allergic and otherwise toxic side effects, but the chemist James Collip was able to adapt and prepare it accordingly at the end of 1921, so that its use on the human organism saved the lives of many diabetics in the years that followed. (6)

1.2 The rising prevalence of Type 2 Diabetes mellitus

According to an estimate based on data from the International Diabetes Federation published in the tenth edition of the Diabetes Atlas 2021, the prevalence of diabetes mellitus at that time was 10.5% or 537 million people worldwide. These percentages were broken down individually to the two biological sexes and it was found that males had a higher prevalence at 10.8% than females at 10.2%.

In the data collection of the IDF, a total of 219 high-quality data from around 215 countries acquired since 2005 up to and including 2020 were incorporated. For countries with less satisfactory documentation estimates were made based on diabetes prevalence in countries with similar economic, ethnic and geographic backgrounds. Overall, this allowed conclusions on the global population aged 20 to 79 years to be captured with a representative value of 93.6% and was therefore included in further calculations.

Data collected through 2021 were further used to provide a potential outlook for estimated diabetes prevalence in 2030 and 2045. With the steadily increasing incidence and type 2 diabetes mellitus occurring earlier and at younger ages, as well as type 1 diabetes mellitus being primarily prevalent in childhood, an increase in numbers over the coming years is no surprise.

If 10.5% or 537 million people are affected by this epidemic in 2021, the figure will rise to 783.2 million in 2045.-Accounting to 12.2% of the total global population. In all these calculations, unfortunately, no specific differentiation was made between type 1 and type 2 diabetes, but it should be noted that type 2 diabetes clearly dominates worldwide with a prevalence of 90%.(7)

These figures seem quite plausible, considering the unhealthy lifestyle prevailing globally in the majority, the associated increase in overweight and obese people, starting in childhood. An additional explanation for the rising numbers is certainly also due to the improved diagnostic methods of modern medicine, which enable early detection. Optimized, individually adapted therapy contributes significantly to diabetics reaching a higher average age, which in turn is reflected in this high prevalence. (7)

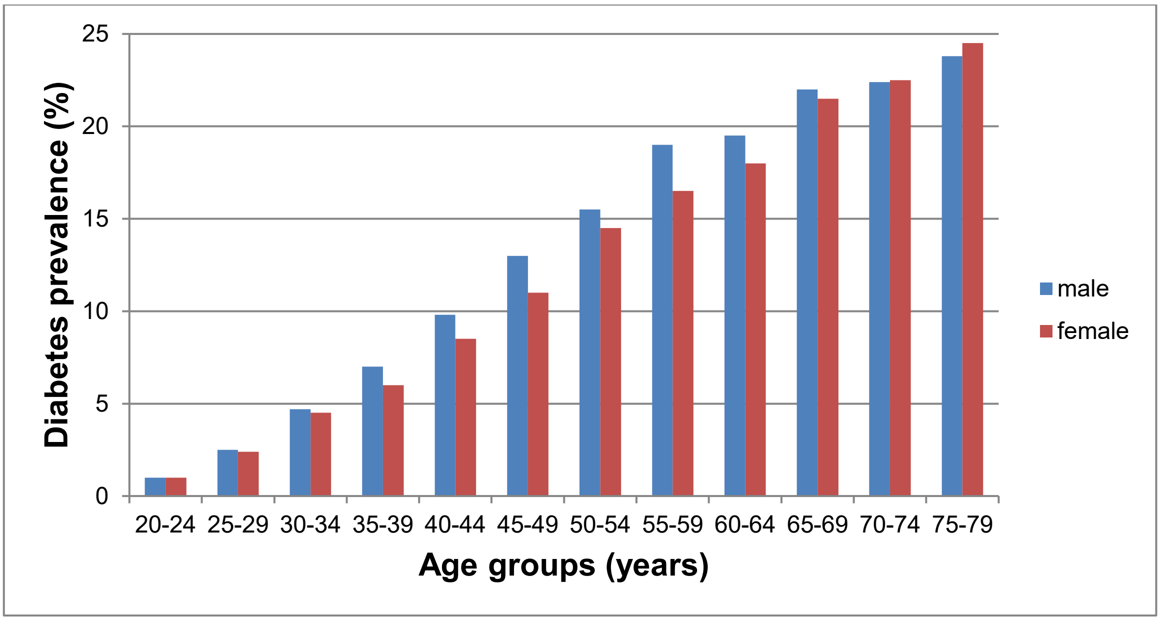

Figure 1: Diabetes prevalence by age and sex in 2021. Adapted from (7)

The data presented in the bar chart above was collected in the International Diabetes Federation Diabetes Atlas, the 10th edition released in the year 2021.

Comparing the results of this data collection, it once more illustrates that diabetes mellitus is a disease that affects both men and women equally.

As shown, it is clear that the diabetes prevalence in 2021 appears to increase, especially with older age. However, according to current forecasts, this picture will soon change as the younger population also becomes increasingly overweight.

Particularly, an unhealthy diet, as well as little exercise in everyday life are the main factors that make this disease gain in prevalence even in modern times.

As stated by WHO records in 1980, approximately 108 million people worldwide were diagnosed with diabetes mellitus -whether type 1 or type 2 was unfortunately not further declared-, this prevalence increased to a total of 425 million in 2017.(8)

According to recent data from 2021, the global prevalence in the 20- to 79-year-old age group was 537 million people. With the rising incidence of overweight and obesity, many of which originate in childhood and adolescence, the prospective numbers calculated using models no longer come as a surprise. For example, 643 million diabetics are expected to be affected by 2030, and 783 million by 2045. (7)

While developing countries with lower basic income have shown rapidly increasing numbers, a particularly high prevalence has already been recorded in industrialized countries, such as Western Europe.

An explanation for this could be more reliable documentation as well as earlier detection in better developed countries. (4, 15)

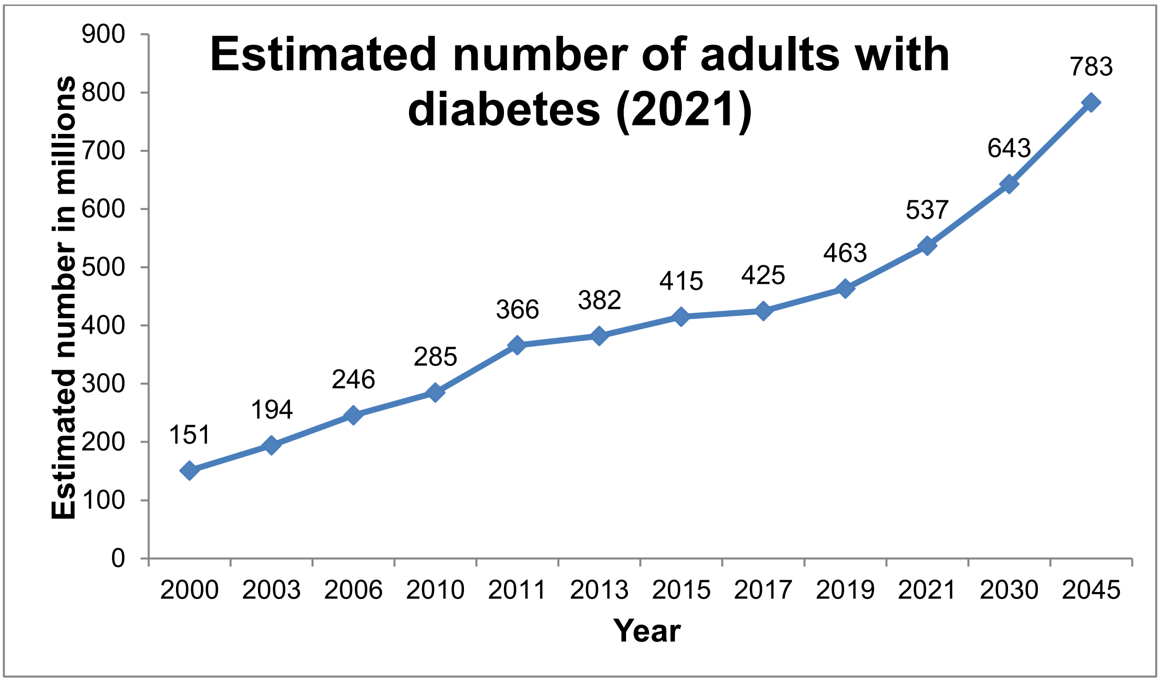

Figure 2: Estimated and predicted number of adults with diabetes worldwide. Adapted from (10)

As published in 2021 on the official homepage of the IDF, the shocking prediction for the future number of people affected by diabetes mellitus is even more strikingly visualised in the chart above.

1.2.1 The current situation worldwide with a focus on the frontrunner China

Looking at the latest listing of the International Diabetes Federation's data from 2021, the global increase in diabetics by country is again made clear.

The first two places each go to China and India, the two countries which currently and according to predictions based on current facts and numbers, will also lead the list for the next decades. China is the undisputed leader with about 140 million diabetics. The reason for this is not only the strong growth of the Chinese population or the fact that the population as a whole is getting older, but above all the unhealthy Western lifestyle that is becoming increasingly established there: fast food, sugary soft drinks and a decrease in overall physical activity. This obesity-promoting behaviour is particularly evident among the urban population. (7, 11)

However, the fact that genetics and ethnicity are also significant factors in the genesis of T2DM is especially demonstrated by the example of China. According to a multi-ethnic study conducted in 2009 with 6814 patients including Caucasians, African Americans, Hispanics, and Chinese adults, aged 45-84 years, it could be shown that Chinese people were already diagnosed with a BMI of 23.7 kg/m² on average. Comparing the average BMI that US Americans had at diagnosis, this was much higher at over 27 kg/m². (12)

Consequently, it has been shown that Chinese have an increased risk of developing T2DM at a lower BMI. This conclusion mainly rests on the fact that the eastern native Asians store excess fat primarily visceral, meaning around the abdominal organs. (13)

In an internationally conducted study on the distribution of intra-abdominal adipose tissue it could even be proven that eastern Asians tend to have the most visceral fat, which also has an impact on the secretion of adiponectin.(11)

Furthermore, multiple studies have demonstrated, that smoking is a significant risk factor for developing T2DM.(14)

Therefore, it is even more serious that over 300 million people in China are active smokers. In particular, male Chinese are strongly represented amongst smokers. On top of that, the number of passive smokers must also be taken into account. In sum, it is assumed that 530 million people are exposed to these harmful fumes. (15)

	2021			2045	
Rank	**Country**	**Diabetics (numbers in million)**	**Rank**	**Country**	**Diabetics (numbers in million)**
1	China	140.9	1	China	174.4
2	India	74.2	2	India	124.9
3	Pakistan	33.0	3	Pakistan	62.2
4	USA	32.2	4	USA	36.3
5	Indonesia	19.5	5	Indonesia	28.6
6	Brazil	15.7	6	Brazil	23.2
7	Mexico	14.1	7	Bangladesh	22.3
8	Bangladesh	13.1	8	Mexico	21.2
9	Japan	11.0	9	Egypt	20.0
10	Egypt	10.9	10	Turkey	13.4

Table 1: Top ten countries with the highest number of diabetics (2021 versus 2045). Adapted from (7)

1.2.2 The current situation in Austria

Based on an estimation by the International Diabetes Federation, the number of people affected by T2DM in Austria is currently (January 2023) estimated at around 800 000, but the number of unreported cases and the number of prediabetics could be much higher. In order to enable the earliest possible intervention and thus to curb long-term consequences as soon as possible, the Austrian Diabetes Association and the Austrian Medical Association have set themselves the goal of recording the current data situation in Austria over the next years. (16, 17)

The goal on the one hand is the creation of a register, which documents as precise information as possible about the number of prediabetics, as well as T2DM patients. This in return acts as a more resource-efficient and earlier detection to prevent inevitable long-term consequences.

On the other hand, in the cohort of those already diagnosed with T2DM, the recording of possible comorbidities, such as reduced cardiac function via the measurement of the laboratory parameter Nt-pro-BNP is also promoted.

Furthermore, the experts recommend that the HbA_{1c} value should be included as a screening parameter for prediabetes or undiagnosed diabetes mellitus in the preventive medical check-up, which is available free of charge in Austria once a year from the age of 18 for everyone with social insurance.

To initiate this project, the Austrian Diabetes Association in collaboration with the Austrian Medical Association has designed a study with two cohorts, which will include a total of 2500 patients. These data will be recorded over a period of six months by 90 general practitioners. -10 from each province of Austria.

As this is a prospective study no results are available at the time of writing this thesis. However, in order to obtain an approximate overview of the more precise, gender-specific distribution of diabetes mellitus in Austria, the following table is based on published data from a survey conducted in 2014 by the Institute of Statistics Austria.

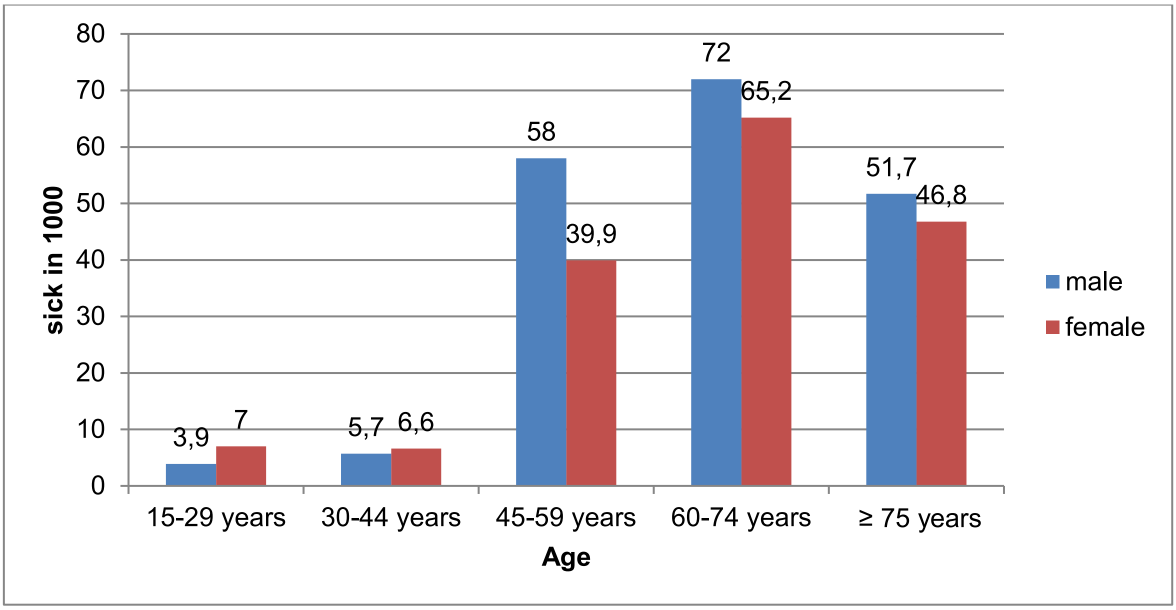

Figure 3: Diabetes in Austria 2014 Adapted from (18)

As can be seen from the bar chart above, it is once more demonstrated that there is no clear gender preference for diabetes mellitus in Austria. This fact could also be observed in other regions of the world even though the latest data from the IDF has shown that overall the male gender has a slightly higher prevalence than the female gender. (10.8% versus 10.2%)

In Austria more women were affected in younger age groups, whereas in older age groups the prevalence seemed to predominate in the male population in 2014.

2 Materials and methods

The present diploma thesis was written by means of literature research under inclusion, as well as consideration of the most current data and studies on the subject of diabetes mellitus type 2, COVID-19, as well as corresponding new promising therapy possibilities in the given context, but also to the established standard therapy scheme.

The main source for this thesis is the medical database PubMed, which presented a useful and time-efficient tool in filtering countless relevant and especially the most recent published studies.

Search terms used included "type 2 diabetes mellitus", "T2DM", "type 2 diabetes therapy", "T2DM Covid-19", "sars cov-2", "Metformin Covid-19", "t2dm mice", "oral antidiabetic drugs", but also the individual substance names of the various oral antidiabetic drug groups.

In addition, the journal "Forum Diabetes" should not remain unmentioned, which gave me the decisive inspiration and idea for the choice of topic for this work. Furthermore, the information contained therein presented the latest findings on the subject of diabetes in a nicely formatted way with each issue.

The preparation of the citations and the creation of the list of sources were supported by the freeware "Zotero".

3 Type 2 Diabetes mellitus and SARS-CoV-2

An emerging virus that has spent the past years presenting unprecedented challenges to all health authorities around the globe is currently the subject of extensive research. First documented in December 2019 in Wuhan Province, China, the new coronavirus, more accurately named SARS-CoV-2, stands for severe acute respiratory syndrome coronavirus 2. The associated clinical symptom complex is globally titled COVID-19. (19)

Initial findings that the virus primarily caused damage to the lungs have since been followed by more detailed investigations. Even if the exact pathophysiological mechanism could not be clarified in detail at the current time (01/2023), it can be roughly said that the virus causes individual systemic inflammatory reactions. (20)

According to multiple studies, an above-average accumulation of COVID-19-infected diabetics could be proven. (21) This now raises the question whether a diagnosed diabetes mellitus favors an infection with SARS-CoV-2 and to what extent such a chronic pre-illness could have an influence on the course, severity and mortality.

The focus in this context will be on studies about type 2 diabetes mellitus, which due to the exorbitantly higher prevalence in contrast to type 1 diabetes mellitus represent the major content of current research.

Already in past epidemics with viral pathogens, an increased infectivity and an associated high incidence in patients with diabetes mellitus could be demonstrated. Nevertheless, it was found that this fact does not automatically apply to infection with the novel coronavirus. Only a clustering of severe COVID-19 courses in individuals with diabetes-associated comorbidities, such as cardiovascular disease, hypertension or obesity could be demonstrated.

However, as a major prognostic factor for the course of a SARS-CoV-2 infection in diabetes mellitus sufferers, it is important to point out the age of those studied. An advanced age is often associated with multiple infirmities, functional impairment of various organs -mostly of the cardiovascular, as well as the renal system- and resulting polypharmacy, which in turn could offer a plausible explanation model for the proven more severe course. (22)

Although, according to an analysis from Italy, of 27 955 people who died from COVID-19 31.1% had diabetes mellitus, which would suggest an association of increased mortality with preexisting diabetes. (22)

This suggestion is supported by further data, such as a survey in England (United Kingdom) of 23 804 included COVID-19 decedents, among whom 32% had prevalent type 2 manifest diabetes mellitus.

A study from the USA with 5700 hospitalized patients with severe disease documented that also obesity (with 41%) or type 2 diabetes mellitus (with 33%) were present as comorbidities with an above average frequency. (23)

According to study data from China, this presumed correlation between obesity and a severe course of COVID-19 is once again confirmed. (24)

However, the most impressive results are provided by a meta-analysis based on data from the first quarter of 2020 (January 1 to April 22, 2020). 33 studies with a total of 16 003 patients were included, which demonstrated a clearly statistically significant association between preexisting diabetes mellitus and a severe COVID-19 course, as well as associated higher mortality compared to metabolically healthy individuals. (25)

From these quite diverse geographic studies, it appears that this increased risk of severe COVID-19 infection exists equally for all ethnic groups with obesity and type 2 diabetes mellitus.

Note that most studies define a severe course of COVID-19 not only as death from the disease, but also with the need of patient admission to an intensive care unit and mechanical ventilation. (26)

This outsized accumulation of SARS-CoV-2 deceased diabetic patients could be explained by the pathomechanism of the coronavirus. Already in studies from March 2020, the angiotensin-converting enzyme 2 receptor could be identified as one of the crucial binding points for the spike protein of the virus. It is through this receptor that the virus enters the human cell. The fact that ACE2 is expressed in multiple organs and tissues, such as lung, heart, kidney, gastrointestinal tract and endothelial cells is all the more serious, which in turn explains the resulting various organ damages of a COVID-19 infection. (27)

The fact that there is an upregulation of ACE2 in adipose tissue is crucial, because this in return means that it affects particularly the obese, insulin-resistant diabetics. This results in an overall higher viral load, especially in the lungs, since the body's ACE2 primarily accumulates there.

Since the ACE2 receptor plays an integral role in the control of the renin-angiotensin-aldosterone system, the associated blood pressure adaptive and organoprotective effects, the virus acts as a significant confounding factor. The resulting imbalance of angiotensin II is accompanied by a lack of antifibrotic, antiproliferative, and antiinflammatory effects. (28)

Via further complex pathomechanisms, a SARS-CoV-2 infection additionally leads to a release of multiple proinflammatory cytokines (interleukins, tumor necrosis factor-α, interferons …). If the human organism is already in an inflammatory damaged state before such an infection due to chronic pre-existing diseases, such as diabetes mellitus, obesity, hypertension, cardiovascular diseases, chronic kidney diseases, etc., the organ damages, which are mainly of vascular nature, are multiplied.

Interestingly, reports also suggest that SARS-CoV-2 infects the pancreatic β-islets, leading to β-cell damage and subsequent new-onset diabetes, severe hyperglycaemia and diabetic ketoacidosis in COVID-19 patients. (29)

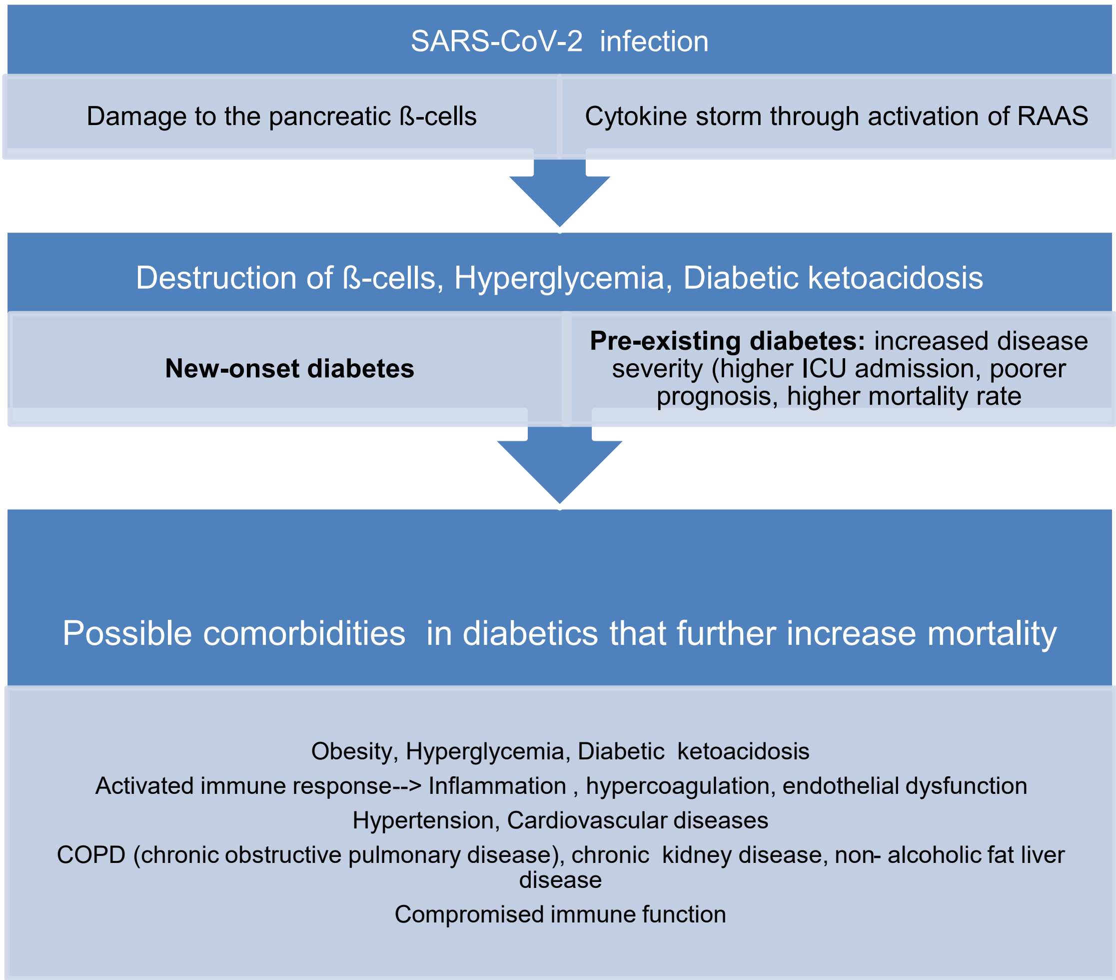

Figure 4: The possible outcomes of a COVID-19 infection with special regards on diabetes. Adapted from (29)

The considerable influence of the prevailing comorbidities on the outcome of an infection with the novel coronavirus was also shown in a study published in November 2020 and conducted in Austria. The actual aim of this study was to predict the in-hospital mortality of patients infected with COVID-19 who already suffered from diabetes mellitus prior to infection and who had a proven prediabetic state.

To calculate this risk, a special score was developed for the 247 hospitalized Austrians included in the combined prospective and retrospective study.

Once more in this study, too, the decisive factors for a poor outcome or increased mortality were, in addition to diabetes mellitus, increased age, cardiovascular diseases, inflammatory signs (CRP), reduced kidney function, and increased liver parameters (ALT). (30)

Thus, the results are again similar to other studies. Even if the individual COVID-strategy and therapy varies within the different countries, it can still be assumed that for all populations with diabetes mellitus and especially diabetic patients with the aforementioned comorbidities there is an increased mortality risk in the context of COVID-19 infection.

3.1 The impact of COVID-19 caused lockdowns and the benefits of physical activity

An integral measure for the prevention of progression or prevention of T2DM is the earliest possible intervention at the lifestyle level. In order to contain the pathological processes in the body associated with obesity, this includes not only a change to a healthy diet - the so-called "Mediterranean diet" is recommended - but above all an increase in daily physical activity.

According to the WHO guidelines concerning the recommended time of physical activity throughout the week, the average person should be active for at least 150 to 300 minutes. However, this time refers to moderate activity levels. For more vigorous intensity aerobic physical activity, the recommended time per week is only 75 to 150 minutes. (31)

The effects of the countless lockdowns and necessary quarantine stays during the COVID-19 pandemic were all the more drastic.

Not only was the average activity level of the global population significantly reduced during this period of sequestration, but even a visit to a doctor's office or hospital was overshadowed by the fear of possible infection with the novel coronavirus.

Thus, essential examinations and controls for early detection of new symptoms indicating diabetes or evaluations of diabetic end organ damage could not take place in a timely manner. The control of a proper HbA_{1c} value and thus the evaluation of an adequate therapy as well as adherence were also neglected during the pandemic.

As already mentioned in the previous chapter **“Type 2 Diabetes mellitus and SARS-CoV-2"**, an increased mortality risk for diabetics suffering from COVID-19 could be proven. All the more important is the factor of regular exercise: moderate exercise not only counteracts obesity, but also offers other health benefits. The positive effects on the immune system and the anti-inflammatory effects of regular, chronic exercise have been demonstrated in various studies. CRP, tumor necrosis factor alpha (TNFα), interleukin-6 (IL-6), and other inflammatory mediators have been significantly reduced as a result.(32)

As early as 2001, these laboratory values were found to be significantly elevated in obese individuals compared to normal weight individuals due to increased expression of these by adipose tissue.(33)

The exact molecular tissue mechanisms that lead to a reduced release of these inflammatory markers have not yet been fully elucidated, but in principle the increased energy demand of the muscles during exercise leads to an increased glucose uptake and a release of IL-6, which is only secreted via muscle contraction.

IL-6 is extremely diverse in its mode of action. The cytokine not only has an inflammatory but also, interestingly, an anti-inflammatory effect. In the mouse model the involvement in multiple signalling pathways mediating the immune system could be demonstrated. The recruitment of T-cells to sites of acute inflammation was mediated via IL-6.

Furthermore, the T- and B-cell differentiation, which is essential for the immune defence, an induction of apoptosis and even accompanying tissue regeneration speak once more for the relevance of the signal molecule.(34)

The knowledge of this training effect alone represents another potent intervention point in the therapy of pre- and manifest T2DM, as well as a possible additional motivation for affected diabetics in the fight against their disease. In particular, early protection against microvascular and macrovascular damage could be provided without the need for pharmacological agents. Accordingly, everyday life would be less affected by side effects without the need to even take medication or with a reduced need for medication. On top of that, the expenses of the healthcare system could be greatly reduced.

4 General principle of therapy for T2DM

4.1 Pathomechanism

In order to develop meaningful new therapeutic methods for a disease, it is essential to understand the basic disease-causing mechanism. T2DM is known to be caused not only by an unhealthy, sugary diet and physical inactivity, but also by complex genetic components.(35)

These genetic predispositions, which primarily collectively lead to impaired pancreatic ß-cell function, are also evident when looking at the prevalence and incidence of different ethnicities. In studies directly comparing light-skinned American and British populations, higher incidence rates emerged in Asians and, ostensibly, in dark-skinned individuals. Due to this population group-specific accumulation, an endogenous involvement in the development of the disease appears to be extremely probable in addition to the known exogenous factors.(35, 36)

It has also been confirmed that inadequately controlled and untreated gestational diabetes not only increases the risk of future T2DM for the mother, but also for the child. The early hyperglycaemic metabolic state results in a predisposition to obesity, and the corresponding compensatory increase in insulin production overloads the ß-cells, which is associated with a subsequent T2DM.(37)

This mechanism is also what leads to an increased risk of T2DM in obese adults.

In order to adapt the high blood glucose level caused by the excessive sugar intake, an equally increased insulin production and secretion is required. Initially, this can still be compensated for by an increase in the work of the ß-cells. However, the longer this stress on the pancreas lasts, the more this leads to an overload of the ß-cells and they eventually perish. This also explains why early lifestyle intervention is so important in obese people. Adaptation of the diet, as well as weight reduction can lead to a recovery of the ß-cells and thus insulin production. Therefore, insulin-dependent T2DM with complete ß-cell destruction can be prevented from manifesting in the first place.

It is also quite interesting to note, that a major contribution to the pathogenesis of insulin resistance is also generated by the hormone-producing effect of excessive abdominal adipose tissue. - An excess of free fatty acids, dysregulation of adipokines as well as the immune system, abnormalities in the intestinal flora and an increased inflammatory response have been identified in affected patients. (38)

Crucial for the development of inflammation and consequently ß-cell damage are the generated reactive oxygen species, briefly referred to as ROS. Oxidative stress has significant impact on complications associated with T2DM. Due to disruption of mitochondrial function, so-called superoxides develop as a toxic metabolic product. This product carries a formative role in the activation of further pathogenetically relevant metabolic pathways.(35)

Especially the so-called AGEs (advanced glycation end products) cause the serious and feared vascular complications of chronically elevated blood glucose.(39)

Thus, two mechanisms are crucial: on the one hand, defective insulin secretion and, on the other hand, impaired insulin sensitivity of the tissue. The resulting insufficient insulin secretion is causal for the hyperglycaemic metabolic state and its subsequent damage to the organs and vessels.(40)

The insulin-controlled uptake of glucose from the blood into the muscles -via the incorporation of insulin-dependent glucose transporters GLUT-4- cannot take place in this form. However, since the cells are dependent on glucose as an energy supplier, glucose supply must take place in a different way. The liver sees this as an incentive to increase gluconeogenesis. The cellular fuel produced in this way cannot reach its target due to the lack of insulin action and remains in the blood. Hyperglycaemia is therefore additionally promoted, resulting in a vicious circle.(35)

4.1.1 Excursus: The gut microbiome and T2DM

The human microbiome currently presents itself as one of the greatest points of interest for contemporary scientists even though highly complex interactions and mechanisms not yet clarified to the last detail.

More and more specific research activities are broadening the knowledge and horizons not only of active researchers but also of the general population. -Mainly due to an increase in advanced technological methodologies, such as mass spectroscopy or DNA sequencing.(41)

But what exactly is the "microbiome" mentioned in multiple studies?

Basically, the knowledge that humans are not the only living organisms in their bodies should not be a novelty. Countless other microorganisms, from bacteria to viruses to fungi, populate each and every one of us. In fact, the human organism is even dependent on these microorganisms: as a prominent example, the lactic acid bacteria (*Lactobacillales*) in the digestive tract may be mentioned here, which are indispensable for the correct metabolism of carbohydrates and thus a physiological digestive function.

A dysbalance of these healthy, symbiotic bacteria has been identified as the cause of many chronic diseases. In addition to cancer and mental illness, pathological influences on metabolism dominate.(42, 43)

Moreover, studies in mice have shown the essential effect of the microbiome on a physiological development of the immune defence and a corresponding anti-inflammatory response.(44)

Based on this fact, several studies have shown a clear association of a defective microbiome with the development of the metabolic disease T2DM.

This in return could also provide a new starting point for therapeutic intervention in the development or progression of this chronic disease.

4.1.2 Potential mechanisms of pathogenesis

Especially the gut microbiome has been shown to play a key role in the development of obesity and thus T2DM. When the delicate balance of intestinal bacteria is compromised by interventions such as long-term or frequent use of antibiotics or a chronically unbalanced diet, the consequences are significant.(45) The effects of an altered composition of the intestinal microbiome can be demonstrated in animal studies as well as in humans.(41)

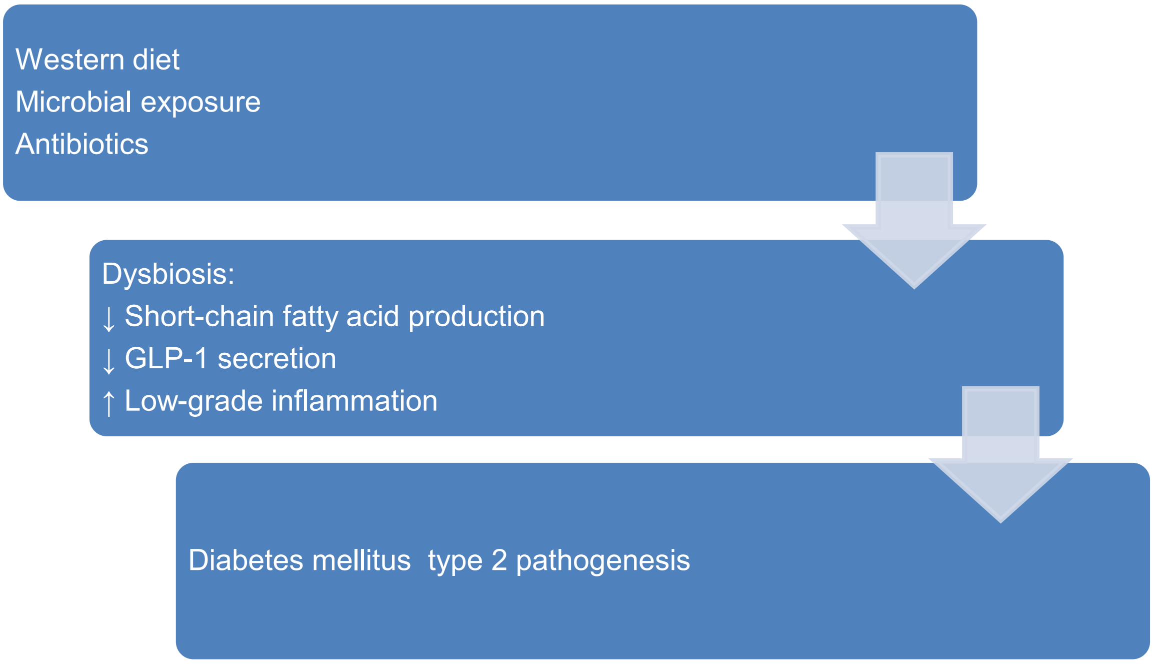

Figure 5: Model of pathogenesis of T2DM. Adapted from (41)

In connection with the genesis of T2DM, the influence of an increasingly unbalanced diet worldwide on the microbiome should be emphasized once again. Not only the increased glucose intake, but also the reduced intake of dietary fibre contributes to this. These polysaccharides, which are indigestible by human enzymes, are fermented only by intestinal bacteria producing short-chain fatty acids (SCFAs) as a metabolic product. While the exact enzymatic pathway is of less interest clinically, the findings that SCFAs exert anti-inflammatory, antitumoric, as well as antimicrobial functions as an important mediator in chemotaxis and phagocytosis are essential.(46)

In addition, this metabolite leads to increased secretion of the antihyperglycaemic glucagon-like peptide-1.(41) This hormone has established its use as an oral antidiabetic in the pharmacological therapy of T2DM in the form of incretin mimetics or GLP-1 receptor agonists.

Several studies have shown that individuals diagnosed with T2DM have a reduced variability of intestinal bacteria.

According to a study from China published in March 2020, an analysis of the individually altered gut microbiome could even predict the risk of developing T2DM.(47)

The diversity and proportionality of the different bacteria is very important in this context. With the two bacterial strains *Bacteroidetes* as well as *Firmicutes*, the consequences of a numerical imbalance could already be presented as the subject of several studies in humans. Thus, it has been suggested several times that a higher number of *Firmicutes* and a lower number of *Bacteroidetes* is associated with obesity and insulin resistance.(48–51)

However, exactly which increase or decrease in bacterial subspecies acts as a predictor for the genesis of T2DM differs from study to study.(47, 52)

Nevertheless, knowledge of an altered microbiome potentially represents a future methodology for early detection of this disease in individuals who are still asymptomatic but genetically predisposed.

4.2 State of the art therapy

4.2.1 Non- pharmacologic treatment

Whether an intervention is necessary and whether these measures are sufficient or not can be assessed primarily by the level of the HbA_{1c} blood value. This parameter should be checked approximately every three months, and if the HbA_{1c} value exceeds seven percent, therapy adaptation should be considered.(53)

The goal should never be strictly only HbA_{1c} reduction, but the patient should be treated individually with all his comorbidities and complaints. An example would be the induction of hypoglycaemia, when blood glucose levels are lowered too abruptly.

In the ACCORD study, as well as the ADVANCE study, the effect of too aggressive blood glucose lowering could be shown. The ACCORD study was originally designed to demonstrate the positive effect of an HbA_{1c} value as close to normal as possible. It should be noted, however, that the participant population consisted of people with a history of cardiovascular disease. Therefore, as a result of radical glucose-lowering therapy hypoglycaemia was probably more frequent for these people, which in turn led to increased all-cause mortality.

In short, these two studies showed that HbA_{1c} alone and its optimization to certain general target values should not be the standard for therapy adjustment. (54)

Nevertheless, there is a certain generally applicable stepwise therapy that is followed in the treatment of T2DM: the base of any adequate treatment and prevention of non-insulin dependent diabetes mellitus, meaning T2DM, is initially non-drug strategies.

If we consider the pathomechanism explained in the previous chapter, we can see why a balanced healthy diet and regular weekly exercise are so essential for preventing and combating this disease.

Since especially overweight people suffer from an increased risk of disease, a correspondingly early intervention on the level of lifestyle is necessary. This includes not only sufficient exercise, as already discussed in chapter **"3.1 The impact of COVID caused lockdowns and the benefits of physical activity"**, but above all an adapted diet.

Dietary recommendations repeatedly mention the so-called “Mediterranean diet”. This refers to a diet that integrates moderate consumption of fish as a source of protein instead of meat. General carbohydrate intake should also be reduced to a minimum. Instead of processed sugars, these should be taken to a limited extent in natural form, i.e. fruit. Complex carbohydrates, which have a lower glycaemic index, are also beneficial for long-lasting satiety and the associated weight loss. Thus, instead of white flour products, it is recommended to rather reach for whole grain cereal products.

Foods with high fibre content are likewise to be preferred for reasons mentioned. In addition to red meat, which has also been shown to increase the incidence of colorectal cancer when consumed frequently, unhealthy trans fats and foods with excess salt content, such as typically convenience foods, should also be eliminated from the diet.(55)

For the intake of healthy fats in the form of fish or olive oil, there is not only evidence of a benefit for T2DM prevention, but above all a positive effect for cardiovascular risk patients, who mainly have dangerous deposits in their vessels caused by hyperlipidaemia and hypercholesterolemia, i.e. by an unhealthy diet.

All these principles are incorporated in the much researched Mediterranean diet. It is considered the most researched diet for curbing T2DM and its corresponding vascular consequences. Its effectiveness has already been demonstrated in multiple studies, such as lowering HbA_{1c} levels and reducing total cholesterol, among others. (56)

The most prominent example is the PREDIMED study from Spain published in 2011. In this parallel-group, multicentre, randomized, controlled clinical trial, which was conducted in primary care centres over five years, a total of 7447 patients with T2DM or cardiovascular disease with three or more risk factors were randomly assigned via computer to one of the three intervention groups.

In addition to two groups on the Mediterranean diet, one with extra-virgin olive oil (n=2543) and the other with nuts (n=2454), the third group (n=2450) was considered a control group with only the instruction to reduce fat intake in their normal diet. Not only were there fewer cardiovascular events, such as myocardial infarctions, strokes, or deaths demonstrated in this context in the intervention groups, but also positive effects on insulin sensitivity, blood cholesterol, oxidative stress, weight and waist circumference. (57,58)

In an adapted study, the so called PREDIMED-Reus nutrition intervention trial, positive effect of the Mediterranean diet on the prevention of T2DM was once more demonstrated. 418 patients were selected, who did not (yet) suffer from T2DM, but had various cardiovascular risk factors. Finally, after four years of follow-up, the test population was screened for new-onset T2DM disease using the criteria established by the American Diabetes Association in 2009. It was found that the incidence of T2DM was reduced by 52% in the Mediterranean Diet group.(59,60)

A more recent randomized-controlled trial that began in 2013 is the PREDIMED-Plus trial, which was designed for over 6 years.

This is a new Spanish trial with the aim of exploring the beneficial changes of extensive weight loss in an at-risk population diagnosed with metabolic syndrome.

This weight loss was primarily induced by a caloric-restricted diet with the Mediterranean Diet, as well as the active promotion of physical activity in the intervention group. In contrast, the control group had to follow a caloric-restricted Mediterranean diet without promotion to increase their physical activity.

Although this study, which included 6,874 participants, was again only carried out with people recruited in Spain, the results nevertheless demonstrated a clear weight reduction and associated lower comorbidities, including those of a cardiovascular and endocrine nature, in the intervention group. This could conclude that such a weight reduction would have equally positive effects for all population groups with similar risk profiles, i.e. the metabolic syndrome, but note that this alone is not scientifically substantiated by this study.

Other positive effects in the form of a reduction in cardiovascular events, HbA_{1c} levels, serum glucose, triglycerides and cholesterol were documented.

Furthermore, it was also shown that inflammatory markers, such as IL-6, TNF-α, among others, jointly responsible for vascular damage, so also in the context of a SARS-CoV-2 infection, could be reduced.

However, it is important to mention that the reduction of the latter two parameters was statistically rather non-significant.(61)

Interestingly, the lowering of leptin, IL-18, and MCP-1, which has proven relevant in diabetic renal changes, were shown to be most statistically relevant in the context of preventing the genesis of atherosclerosis.(62)

These two studies serve as prime examples that consistent lifestyle adaptation can have immense effects on the human organism. Essential is a corresponding trust in the treating physician and a continuous conversion of the new behaviours into the patient's daily routine. Optimally, this change includes not only a healthy diet, but also regular exercise. Of course, the harmful effects of alcohol, nicotine and constant stress in everyday life on the vessels should not remain unmentioned.

A regular and adequate sleep pattern is also essential to start the day full of energy and motivation.

Only with appropriate adherence can the ultimate goal of these first so essential non-drug measures, e.g. weight reduction as well as a better glycaemic control be achieved together with the patient. In the best case, it even spares them from further therapy with pharmacological agents.(60,63)

This in return would on the one hand save the respective cost bearers in the health system innumerable amounts of money, whilst on the other hand it would cause a lot less complications for the afflicted themselves.

Therefore, the right way to fight this “endocrine pandemic” seems to be to focus on education and campaigns regarding self-efficacy and to promote the benefits of sports and nutrition for the prevention of this disease.

4.2.2 Pharmacological treatment

Pharmacological intervention is considered only after all non-drug measures have been exhausted. Generally speaking, this is the case if the HbA_{1c} value is still above seven percent and lifestyle interventions in form of an adapted diet as well as regular exercise have not led to sufficient results after three months.

In any case, the patient's individual situation should be taken into account. Depending on the patient's various comorbidities in addition to the elevated blood glucose level and the degree of damage to the vessels already present at the time of diagnosis, more or less extensive measures are indicated.

For example, in the presence of a metabolic syndrome and associated hyperlipidaemia, the administration of statins or antihypertensive drugs may be appropriate.

For the specific therapy of persistently elevated blood glucose levels, however, the administration of an active substance from the group of antidiabetic agents in the form of monotherapy is started as standard.

The primary goal is to lower blood glucose levels, i.e., to achieve normoglycaemia, and thus to limit the potential consequences of frequent hyperglycaemia, especially at the vascular level. (53)

4.2.2.1 Types of Antidiabetic agents

A basic distinction is made between insulinotropic and noninsulinotropic antidiabetic agents. While the former promote insulin secretion from the β-cells directly at the pancreas, the noninsulinotropic groups achieve their effect via other organs, such as the gastrointestinal tract and via mechanisms other than just increased insulin secretion.(64)

An effect of these drug groups is therefore only possible if the pancreas still has sufficient ß-cells for insulin production. Consequently, no effect of these substance groups will occur in the case of type 1 diabetes mellitus, pancreatectomy or a pancreas which has been severely damaged by COVID-19.

Class	Agents
GLP-1 agonists ("incretin mimetics")	• Exenatide • Liraglutide • Semaglutide • Dulaglutide •
DPP-4 inhibitors ("Gliptins")	• Saxagliptin • Sitagliptin • Linagliptin •
Sulfonylureas	First generation • Chlorpropamide • Tolbutamide Second generation • Glyburide • Glimepiride • Glipizide •
Meglitinides ("sulfonylurea like")	• Nateglinide • Repaglinide

Table 2: Insulinotropic agents. Adapted from (64,65)

Class	Agents
Biguanides	• Metformin
SGLT-2 inhibitors	• Canagliflozin • Dapagliflozin • Empagliflozin
Alpha-glucosidase inhibitors	• Acarbose • Miglitol
Thiazolidinediones ("Glitazones")	• Pioglitazone • Rosiglitazone •
Amylin analogs	• Pramlintide

Table 3: Noninsulinotropic agents. Adapted from (64)

4.2.2.1.1 Insulinotropic agents

4.2.2.1.1.1 Sulfonylureas and Meglitinides (“sulfonylurea like”)

Sulfonylureas are one of the oldest oral antidiabetic substance groups. As early as 1942, a desirable hypoglycaemic effect was observed in animal experiments and by the 1960s it became already available on the market in pharmaceutical form to the general public for appropriate therapeutic purposes. As shown in Table 3 there are two generations of sulfonylureas, although nowadays only the second generation is used, since these substances simply have more favourable pharmacokinetics in addition to a longer duration of action. (66)

The effect of this substance group takes place via the so-called SUR-1, which stands for the sulfonylurea receptor-1, of the potassium channel in pancreatic ß-cells. This ATP-sensitive receptor, when bound to it, leads to closure of the potassium channel, which in turn results in membrane depolarization of the cell. In the further course, voltage-dependent calcium channels are opened, which leads to an increased release of the insulin supply stored intracellularly in granules. (52, 64)

The Meglitinides also exert their effect by inhibiting the potassium channel in ß-cells, but have a somewhat different chemical structure than the sulfonylureas originally developed.(53)

In addition to the desirable effects of increased insulin release and corresponding lowering of blood glucose levels, the sulfonylureas and their derivatives have come somewhat into disrepute due to significant side effects, such as undesirable weight gain due to increased glucose uptake, as well as dangerous hypoglycaemias.

These hypoglycaemias can occur particularly easy if patients eat irregularly or take the antidiabetic drugs only in the evening without subsequent adequate glucose intake.

This makes it all the more essential to monitor blood glucose closely and to adjust the dose of antidiabetic drugs accordingly, especially in the context of COVID-19.

Depending on the severity of the infection, the critically ill patient will certainly consume less food and the highly febrile patient will have higher energy expenditure. (52, 64)

However in studies, the use of sulfonylureas in the setting of a SARS-CoV-2 infection has not yet proven to have a benefit in terms of mortality. Nevertheless, the usage also does not result in an increased mortality, which leads to the result that this group of drugs has been classified as "neutral" for diabetes therapy under COVID-19. (67)

4.2.2.1.1.2 GLP-1 agonists (“Incretin mimetics”) and DPP-4 inhibitors (“Gliptins”)

The incretin mimetics as well as the gliptins, which first appeared on the European market around 14 years ago, are considered to be a rather younger group of substances with a blood glucose-lowering effect.

Incretins are basically hormones that are produced in the intestinal mucosa and secreted when the blood glucose level is increased, especially postprandial due to food intake. Secretion practically only occurs with a corresponding stimulus, i.e. elevated blood glucose, which has the great advantage that in contrast to the sulfonylurea like antidiabetics no hypoglycaemia can occur. (53, 68)

Also noteworthy is a phenomenon commonly referred to in literature as the "incretin effect": It has been found that oral glucose intake leads to double to triple insulin secretion compared to parenteral glucose intake. However, it now seems all the more essential to recognize that this incretin effect, which is so beneficial, becomes increasingly ineffective in individuals in the setting of T2DM. The effect of GIP is lost, but that of GLP-1 is usually still preserved. Based on this fact, the idea was born to develop drugs that promote the beneficial effects of GLP-1: the incretin mimetics.(68, 69)

Binding to the corresponding receptors of the pancreatic β-cells leads to a reduction in blood glucose levels via the resulting increase in insulin secretion. The hormone GLP-1 also has an effect on the α-cells of the pancreas: glucagon secretion is reduced, which can be described as an antagonist of insulin. This stops a reflex glucagon-induced increase in blood glucose levels, primarily generated via gluconeogenesis and glycogenolysis in the liver. Thus, the blood glucose level is indirectly lowered. (70)

In order to maintain a natural body function, GLP-1 is already degraded after a few minutes by enzymes, first and foremost DPP-4. For this reason, the chemical structure of the medically used GLP-1 agonists is modified accordingly so that they are not affected by the degradation of these enzymes. This results in a longer blood glucose-lowering duration.

The mechanism of action of DPP-4 inhibitors is therefore self-explanatory: by inhibiting the degrading enzyme DPP-4, a prolonged effect of GLP-1 is achieved.

In addition to the insulinotropic effect, the appetite-suppressing effect mediated by GLP-1 receptors in the brain proves particularly attractive. (68)

Another effect that contributes to a longer lasting feeling of satiety and thus to a reduction in appetite and the desired weight loss is the slowing down of the passage of food through the intestines.(71)

It is therefore not surprising that GLP-1 agonists in particular, such as Liraglutide, are increasingly being used as slimming agents, especially in times of COVID, where physical activity has decreased sharply, even further aggravated through the numerous lockdowns, as already discussed in Chapter 3.1.

There are a number of studies on Liraglutide in particular which have shown that in addition to the benefit of lowering blood glucose significant weight loss can also be achieved.

For example, the phase III study NN8022-1807, in which the effects on the weight of initially 564 obese European study participants selected according to pre-criteria were demonstrated. The weight reduction was compared on the one hand with the application of Liraglutide in various doses, and on the other hand with the effect of the active ingredient Orlistat, which has already established itself as an appetite suppressant, and the effects of the application of a placebo. It could be shown that the weight loss was greatest with continuous application and accompanying lifestyle modifying measures with Liraglutide 3.0 mg.(71)

Another study, the so-called SCALE Maintenance trial, built on the previously described findings tested Liraglutide 3.0 mg versus placebo. Not only did the subjects on Liraglutide achieve greater weight loss, but it was also shown to be longer lasting than the weight loss in the placebo group. The positive effect on blood glucose was also demonstrated by means of the HbA_{1c} value. Furthermore, the development of T2DM was also shown to be reduced with Liraglutide 3.0 mg compared to placebo alone: after three years of study duration, 1.8% of the study participants with a pre-existing prediabetes developed a manifest T2DM with Liraglutide, whereas 6.2% of the people taking a placebo preparation developed this dangerous metabolic disease at a significantly higher rate. (71)

Although the weight loss, lowering of blood glucose levels, and above all the reduced development from prediabetes to a manifest T2DM are groundbreaking results, especially with the additional cofactor of an aggravated COVID-19 disease progression in individuals affected by T2DM, the side effects of this class of agents should also always be pointed out as it should be the case with any drug. - Especially before any first time application.

The main problems are frequently caused at the beginning of use by the prolonged gastric passage and manifest themselves primarily as gastrointestinal complaints, such as abdominal pain, nausea, vomiting and diarrhoea. The development of pancreatitis is also reported as a serious side effect in some literature sources. Hypoglycemia generally occurs only in combination with sulfonylureas, which is why this combination is not recommended.(67, 71)

In principle, these two substance groups, i.e. the GLP-1 agonists and the DPP-4 inhibitors, are most commonly used in combination with other antihyperglycaemic substances, especially when sufficient blood glucose control can no longer be achieved with the first-line therapeutic metformin alone. (68,72)

A distinction can be made between short-acting GLP-1 agonists, which have to be injected daily into the subcutaneous adipose tissue, and longer-acting GLP-1 agonists, for which an injection only once a week is sufficient.(72)

With regard to the use of GLP-1 agonists or DPP-4 inhibitors in the context of an infection with SARS-CoV-2, the data available at the time of writing this paper is extremely insufficient to derive generally valid statements.

In relevant sources of pubmed, the authors agree that GLP-1 agonists, as well as DPP-4 inhibitors also show anti-inflammatory effects. Therefore, in addition to weight reduction and blood glucose lowering they could have a protective effect in the context of a COVID-19 disease, but there are still no significant, larger studies to support this fact. (73)

The data situation regarding DPP-4 inhibitors is particularly interesting in that DPP-4 as well as ACE-2 serve as entry points for SARS-CoV-2. At least in in vitro studies it could be demonstrated that the entry of the virus into human cells could not be relevantly reduced by inhibition of the DDP-4 enzyme. (73,74)

4.2.2.1.2 Noninsulinotropic agents

4.2.2.1.2.1 Biguanides

The typical first-line therapy for overweight diabetics with preserved insulin secretion today is primarily the biguanide metformin. This has been an integral part of type 2 diabetes therapy since the mid-1950s. With its not only antihyperglycaemic but also appetite-suppressing effect, it seems to be an optimal combination.(53)

The blood glucose-lowering effect results from multiple mechanisms: in addition to decreased release of glucose from the liver, i.e. glycogenolysis, via inhibition of gluconeogenesis, glucose uptake in the intestine is also inhibited.

Furthermore, insulin sensitivity is improved via increased insulin binding to the corresponding receptor, and insulin action on glucose transporters is enhanced. This in return means a normal insulin secretion is a requirement for action.

These mechanisms enable metformin, which is often referred to as an "insulin sensitizer," to ensure increased glucose uptake from the blood into the tissue.(53)

In the context of a therapy of diabetics suffering from COVID-19, the positive effects of blood glucose lowering by means of metformin could be demonstrated, as described in more detail in chapter 7.

4.2.2.1.2.2 SGLT-2 inhibitors

A comparatively young group of substances are the SGLT2 inhibitors which got first approved in the USA in 2013. (75)

The decisive idea for the development came from the analysis of natural substances, more specifically the flavone glycoside phlorizin extracted from tree bark, which led to the desired blood glucose reduction in diabetics through increased blood glucose excretion via the urine.

The exact effect is based on an inhibition of sodium-glucose cotransporter-2 in the proximal tubule of human nephrons, which is mainly responsible for glucose reabsorption. This inhibition results in reduced reabsorption and increased urinary glucose excretion, i.e. drug-induced glycosuria. This also has a positive effect on the weight of patients due to the beneficial blood glucose reduction and inhibition of absorption. (53)

What makes the SGLT2 inhibitors such a promising group of substances are numerous studies, for example the EMPA-REG OUTCOME study with empagliflozin, the CANVAS study with canagliflozin, or the DECLARE study with dapagliflozin. These studies underline the additional cardio- and renoprotective effects of this group of substances. Glycosuria is accompanied by an osmotically induced diuresis, i.e. increased water is excreted with the glucose, which has an antihypertensive effect.

The use of this drug led to a reduced number of major adverse cardiac events, but also to a significant reduction in hospitalizations due to heart failure. Similarly, the use of these oral antidiabetic agents reduced the progression of renal insufficiencies.(76,77)

These findings suggest that SGLT2 inhibitors should especially be used in diabetic patients with cardiac or renal comorbidities, often in combination therapy with metformin.

Based on these facts, it would be obvious that this particular group of noninsulinotropic agents could have possible protective effects in the case of general inflammation and subsequent organ damage in the context of an infection with SARS-CoV-2. In addition to the aforementioned cardiorenoprotective effects, a reduced expression of inflammatory substances, such as cytokines, chemokines, and certain interleukins, could also be observed. Nevertheless, these positive effects must always be evaluated in comparison with potential negative effects. Indeed, glycosuria leads to an undesirable culture medium for bacteria and fungi in the urogenital region. In the worst case, this can lead to a so-called Fournier gangrene.(78)

The diuretic effect, which initially appears to be beneficial in the treatment of hypertension, is also rather problematic, especially for severe cases of COVID-19.

Since patients are more easily dehydrated by the fever and the lack of hydration provoked by weakness, this can subsequently lead to kidney damage or even acute kidney failure.(79)

It is also essential that euglycaemic diabetic ketoacidosis can be provoked under SGLT2 inhibitor therapy especially under reduced food intake, pancreatitis, physical stress due to surgery, trauma or during critical illnesses such as COVID-19.

This is a result of reduced carbohydrate concentration in the blood and volume loss due to drug-induced glycosuria. The body is in a state of starvation and secretes corresponding anabolic hormones such as glucagon or cortisol.(80)

Therefore, the group of substances should be used with appropriate caution during a SARS-CoV-2 infection. Further study results in this context remain to be seen in order to be able to make a reliable statement regarding the advantages and disadvantages of an application.

For example, the DARE-19 study, an international randomized double-blind placebo-controlled study with dapagliflozin (10 mg), which was used daily for a total of 30 days in infected, hospitalized patients, set its goal to demonstrate a possible reduction in disease complications, as well as mortality in the context of COVID-19.

Even though the study population, which took the dapagliflozin had fewer numbers of severe organ failure and deaths these observations were not statistically significant.

Although the hoped-for benefits of using dapagliflozin did not prove relevant in this study, the following recommendation can still be noted: an antihyperglycaemic therapy with SGLT2 inhibitors which was already well established before an infection with SARS-CoV-2 should still be continued in a monitored manner during a COVID-19 disease in people diagnosed with T2DM. (81, 82)

4.2.2.1.2.3 Alpha-glucosidase inhibitors

The following group of active ingredients exerts its effect via the human intestinal tract, namely as a competitive inhibitor of the luminal, membrane oligosaccharidase in the small intestine called alpha-glucosidase.

These enzymes are responsible for the cleavage of polysaccharides ingested with food, which must first be broken down into usable monosaccharides, such as glucose, before they can be absorbed by the body. The ingestion of food results in a flood of polysaccharides, which are enzymatically broken down in the intestine and subsequently absorbed by the body.

This results in an enormous increase in blood glucose levels postprandial, which can lead to hyperglycaemia in individuals with impaired insulin secretion or insulin resistance. The fact that regular hyperglycaemia has a negative effect on the vessels and subsequently on the organs of a person has already been elaborated many times in this thesis, and therefore the benefit of alpha-glucosidase inhibitors can also be derived.

Especially in type 2 diabetics, who are often conspicuous by a particularly high carbohydrate diet, the postprandial sugar high can be lowered by enzyme inhibition. In this form, the undigested sugar cannot be absorbed by the body, but nevertheless continues to migrate through the intestinal tract.

After the carbohydrates cannot be broken down in the small intestine as physiologically predetermined by the body due to the enzyme inhibition, they continue undigested into the colon. However, the microbial flora predominating there finally breaks down the polysaccharides that are still unabsorbed. Although this results in delayed degradation, thus delayed sugar absorption and a more evenly distributed rise in blood glucose levels, the bacterially induced decomposition in the colon also has its negative side effects.

Particularly when large quantities of carbohydrates are broken down in the lower intestinal tract with a delay, patients complain of undesirable gastrointestinal side-effects such as diarrhoea, flatulence, abdominal pain, and nausea or vomiting. (52, 74)

In addition, the active ingredient acarbose in particular is shown to be responsible for clinically documented liver damage in a publication presented in January 2021. This microbial produced oligosaccharide was first approved in the United States in 1995 as an antihyperglycaemic drug. (83)

However, the additional effect of an increased release of the incretin GLP-1 should be noted as positive. The resulting enhancement of the overall antihyperglycaemic effect is described in more detail in the corresponding subsection **"4.2.2.1.1.2 GLP-1 agonists (“Incretin mimetics”) and DPP-4 inhibitors (“Gliptins”)"**. (84)

It is also important to recognize a reduction in the HbA_{1c} value, which functions more or less as a reference value for long-term damage caused by elevated blood glucose levels.

The intake of the substance group discussed here should always take place before a meal in patients with correspondingly documented postprandial hyperglycaemia, i.e. as a rule three times a day, in order to contain the subsequent absorption with accompanying excessive blood glucose levels.

In practice, this short interval between doses also proves to be restrictive and tedious for patients. For example, with the more modern GLP-1 agonists (e.g. dulaglutide), it is sufficient to inject them subcutaneously once a week. (72)

It is therefore not surprising that the active ingredient acarbose in particular is increasingly being replaced in the treatment of T2DM by more effective and more convenient alternative active ingredients due to the often very unpleasant side effects for the patient.

Nevertheless, the enormous potential of this entire substance group should not be forgotten, as a paper published in January 2022 with the significant title *"Acarbose is again on stage*" argues for a comeback of this substance. Significantly, study results show that the simultaneous increase in GLP-1 secretion is particularly effective in reducing dangerous abdominal adipose tissue. (85)

In the so-called *"Acarbose Cardiovascular Evaluation"* study, a randomized controlled trial, it was also shown that a reduction in the development of manifest

T2DM was observed among the included population taking the active substance acarbose compared with placebo.

Unfortunately, this study cannot be considered globally representative, as the 6 522 study participants were all of Chinese descent. Nevertheless, it should also be mentioned that the included participants already suffered from prediabetes in the sense of postprandial elevated glucose levels, as well as from previously known coronary problems.(86)

It therefore remains to be seen whether further studies with more diverse study participants will be able to make generally valid statements in this context.

With regard to the use of alpha-glucosidase inhibitors in connection with COVID-19, a meta-analysis published only recently in March 2022 was able to demonstrate that this substance group does not represent an advantage in reduced mortality in T2DM and a SARS-CoV-2 infection. Taking acarbose did not reduce mortality, but conversely did not significantly increase mortality in individuals with T2DM. This substance group can therefore be considered neutral in this respect. (65, 79)

4.2.2.1.2.4 Thiazolidinediones ("Glitazones")

The following group of oral antidiabetic agents acts directly in the nucleus of fat cells, the so-called adipocytes. Via stimulation of the nuclear PPAR-gamma, the peroxisome proliferator-activated receptor gamma, through binding to the DNA the substance thereby directly influences further transcription and translation, especially in regard to the fat metabolism.

However, the effect of this group of drugs therefore only occurs with a strong delay after about one to two months. Furthermore the result is a redistribution of fat. From visceral adipose tissue to the periphery since the main target of the pharmacological substance are the peripheral adipocytes. More proteins are formed, which lead to an increased triglyceride storage, for example fatty acid transporter proteins or fatty acid binding proteins, whereby less fuel remains for the formation of a hyperglycaemic metabolic state.

In order to be able to provide sufficient energy, the body must therefore make increased use of freely circulating glucose. This can also be progressively absorbed into the cells by the additionally resulting increase of incorporated GLUT-4 transporters. Furthermore, the thiazolidinediones also cause a change in the hormone secretion of the adipocytes. An insulin-sensitizing effect results from an increased adiponectin production and a reduced TNF-alpha production.(53,88)

However, the increased fat intake has a negative effect on the human body in the form of weight gain. Not only is there increased storage of peripheral fatty tissue, but there is also retention of fluids which, manifested primarily as edema, can cause cardiac problems. Therefore, the use of this substance group is not recommended in patients with heart failure of any NYHA class due to possible decompensation. Heart failure is thus a contraindication.

Similarly, some cases of severe hepatitis up to liver failure have been documented under the use of glitazones, which is why monthly monitoring of transaminases should be performed. (89)

As a positive effect, however, it should be mentioned that the increased fat storage in the peripheral adipocytes apparently results in fewer fatty deposits in the vessels. This is the result of several studies in patients taking the substance pioglitazone. By lowering LDL cholesterol and increasing HDL cholesterol, atherosclerotic plaques can be reduced, thus limiting concomitant diseases such as hypertension and the resulting endothelial damage. (90)

It has also been shown, quite independently of diabetes mellitus, that pioglitazone can also be attributed positive effects directly on the human heart. In studies, for example, it led to increased systolic and diastolic heart function.(90)

Nevertheless, glitazones should be prescribed with great caution. Another serious side effect was shown to be an increased risk of developing bladder cancer which was found in some individuals and associated with an intake of glitazones. Accordingly, patients with corresponding risk factors for the development of bladder cancer, such as regular smoking of cigarettes or predisposing genetics, should not be prescribed glitazones. (52, 80, 81)

With regard to a possible benefit in the use of thiazolidinediones in patients suffering from COVID-19, it can be stated that these have a vasoprotective and also anti-inflammatory effect. Still caution should be taken, because due to the fluid retention especially the lungs are additionally damaged in severe cases of novel coronavirus disease. (73)

One study suggests that this anti-inflammatory component of pioglitazone, when administered at a low dose of 15 mg per day, could potentially provide a benefit in a SARS-CoV-2 infection by lowering inflammatory TNF-alpha or IL-6, but this still needs further investigation. (92, 93)

More complex mechanisms also cause an increase in membrane-bound ACE2, which acts as the docking site for SARS-CoV-2. However, it is only a hypothesis that this provokes an increased susceptibility to infection, but this could be a potential explanation for why the thiazolidinediones, despite their effects, which at first glance only appear to be beneficial, did not show any benefit in terms of mortality in COVID-19 cases in studies.(67)

An article published in March 2021 in the science magazine "The Lancet" again shows a slightly reduced mortality rate per 1000 patient-years under the use of thiazolidinediones and COVID-19 related mortality. A more detailed breakdown of the patient population also illustrates the cardiovascular protective properties of this substance group: especially among those study participants with previously known cardiovascular problems COVID-19-related mortality was most obviously reduced with an adjusted hazard ratio of 0.69. The study was also able to show a slight reduction in the mortality rate per 1000 patient-years. (87)

However, it is mentioned several times that the group of substances discussed in this chapter should not be used in very severe novel corona cases, i.e. critically ill patients with necessary supervision in intensive care units, due to fluid retention and the associated edema formation (73,93)

Thus, in order to be able to make generally valid statements regarding the preponderance of advantages or disadvantages, it remains to be seen whether further studies will be conducted on the basis of these initially partly diverse study results.

5 Vaccination

One strategy has proven effective in the fight against many infectious diseases: the development and widespread use of vaccines. This was also the case for the containment of SARS-CoV-2, or so it was initially thought. It soon became apparent that the RNA virus with its spike proteins mutated in many cases and that the vaccines developed did not provide 100% protection against infection.

Nevertheless, some studies have shown that vaccination offers protection against transmission of SARS-CoV-2. - Among others, two studies from England and Scotland, which were published in 2021, led to this conclusion. The number of infected people in a household with a confirmed SARS-CoV-2 infection was compared with vaccinated versus unvaccinated individuals. Through this study, it could be impressively shown that already a single vaccination dose of the ChAdOx1 nCoV-19 (AstraZeneca) or BNT162b2 vaccine (Pfizer–BioNTech) led to a 40-50% lower risk of transmission. (101)

Since at that time primarily the alpha variant of the coronavirus was prevalent, these statements can only be derived for this original variant.

However, it is important to note that vaccination protects against a more severe course of the disease and any resulting organ damage. This in turn reduced the number of hospitalizations required for COVID-19 patients and thus relieved the burden on the healthcare system.

Unfortunately, these crucial effects of vaccination no longer seem to be as effective with respect to the newer Omicron variant of the virus, which is why the development of an adapted vaccine is useful. The results of this will need to be determined in future studies. (102)

It should also be mentioned that protection by vaccination is strongly dependent on the vaccine itself, be it AstraZeneca or Pfizer-BioNTech and furthermore on the number of boosters, in addition to the virus variant. (103)

In the given context, the question of the effectiveness of vaccination in diabetics who, as already mentioned many times, have an increased risk profile in the context of a SARS-CoV-2 infection, is of course even more interesting.

This crucial question has been addressed by research teams at the Medical University of Graz and the Medical University in Innsbruck, among others.

Their study, published in January 2022, compares the reaction of the body's own immune system of healthy individuals with the immune reaction of diabetes patients.

Anti-spike protein antibodies were measured one to two weeks after vaccination. In addition to a control group of 86 healthy individuals, the test collective consisted of 150 diabetics, 75 of whom had type 1 diabetes mellitus and 75 with type 2 diabetes mellitus.

While after the first vaccination dose in both diabetic groups only 50% (52.7% of the type 1 diabetes group and 48.0% of the type 2 diabetes group) of the study participants reached an adequately high antibody concentration, after a second vaccination dose an equally high antibody concentration could be detected in all three comparison collectives.

As this study is still ongoing, further officially available publications on the observation of the humoral response after a third or even fourth vaccination dose are still pending from this research group.

Nevertheless, based on the data available so far, the important finding has already been demonstrated: the immune response of diabetics to vaccination appears to be the same as in healthy individuals which in turn allows the conclusion that vaccination of this risk population would be highly recommended.(104)

6 New potential therapeutic methods

Intensive research into new antidiabetic or antihyperglycaemic substances is being conducted not only in connection with COVID-19. Of the currently approved substance classes for the therapy of T2DM the newer SGLT2 inhibitors, GLP-1 receptor agonists, and DPP4 inhibitors are convincing due to their additional cardiovascular and renoprotective effects.

6.1 Animal testing, new intervention points and mechanisms

The identification of new therapeutic methods in the global struggle to curb T2DM is subject to tremendous scientific interest. However, specific substances, diets, or interventions at the molecular level, which have already proven their efficacy in animal studies, unfortunately often cannot be directly inferred to have the same efficacy in the human organism.

Potential was shown by the use of inorganic nitrate (NO3-) as well as nitrite (NO2-) in animals. The basic idea for the application of these molecules is based on an impaired effect of the important biological messenger nitric oxide NO. In addition to controlling a wide variety of physiological signalling pathways, its vasodilatory effect is essential for adapting perfusion at the cardiovascular level.

This in return is not only beneficial for blood pressure control, but also for the prevention of ischemia in subsequent organs, for example during heavy physical exertion which is usually accompanied by a higher oxygen demand. In connection with the genesis of T2DM, NO has also been assigned a crucial role in the control of glucose and insulin homeostasis. Indeed, the neurotransmitter also acts as a crucial mediator of insulin secretion. (105)

From an unhealthy, high-fat diet with a deficit of physical activity, the metabolic syndrome develops including all its facets: oxidative stress, consequently the release of inflammatory particles, as well as a substantially reduced NO production and bioavailability. (106)

All these factors, especially the lack of expression or production of NO due to impaired eNOS contribute significantly to the development of hyperglycaemic metabolic state and subsequent T2DM.

Thus, the idea of selectively supplying NO from exogenous sources arose. NO3- and NO2- represent essential resources for the production of nitric oxide.

In animal experiments performed on appropriately modified rats, a positive effect on glucose and insulin metabolism after supplementation could be demonstrated: an improvement of insulin sensitivity via increased GLUT-4 expression, positive effects on lipid metabolism and dyslipidaemia, which is essentially pathologically causative in the metabolic syndrome, reduction of the oxidative stress state and the accompanying inflammatory response had a promising effect in several experiments. (107–109)

Even increased insulin secretion and production could be recorded in nitrite-treated rats. (110)

Another promising effect relates to the so-called "browning" of adipose tissue. This transformation of white adipocytes to brown adipocytes was observed in an experimental study with rats suffering from T2DM on the one hand and a healthy control group on the other hand after application of drinking water mixed with 100 mg/L sodium chloride continuously for six months.

These findings were clarified in the comparison with two untreated groups, again a collective of diabetic rats and healthy rats, which were fed exclusively normal drinking water over the same period. At the endpoint of the study, there was a fat- and weight-reducing effect in the nitrate-treated animals, which could prove therapeutically relevant in the therapy of T2DM in humans via an increased expression of browning genes. (111)

In another experimental animal study in mice, the metabolic as well as cardiovascular effects were compared when metformin (150 mg per kg per day) was administered and when sodium nitrate (85 mg per kg per day) was administered. Since biguanides are still the first-line therapy for T2DM along with dietary and lifestyle adaptations, a comparison with this substance seems plausible.

The findings obtained are quite interesting: it turned out that the desired blood glucose-lowering, antidiabetic effect of metformin was equally present in the therapy with sodium nitrate.

In a direct comparison, nitrate was even more convincing than metformin: in addition to the positive effects on glucose and insulin metabolism, the vasodilator component of NO generated from nitrate acted accordingly against hypertension, which is a common comorbidity in T2DM-damaged vessels. With nitrate intake a reduced accumulation of adipose tissue in the liver was recorded. (106)

However, possible side effects of nitrate and whether this efficacy also exists for humans will have to be proven in controlled clinical trials.

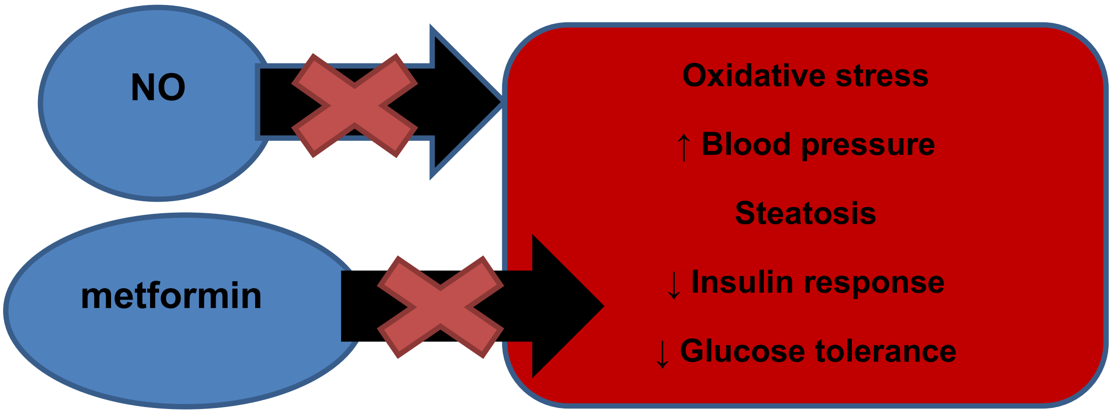

Figure 6: Therapeutic effects of NO application in a study on rats. Adapted from (72)

This flow chart once more displays the enormous potential of NO as it was perceived in the cited study. Whereas metformin has known positive effects on insulin response and glucose tolerance, NO impresses even further with its additional benefits on high blood pressure, steatosis, oxidative stress besides its effects on insulin and glucose levels.

These results were demonstrated at least in the rats in this study.

However, it is essential to recognize that for the exogenously supplied nitrogen sources to be converted into NO that can be utilized by the human body there must be sufficient functionality of the eNOS. (112)

In addition, it was found that an interaction between ingested food and the artificially supplied nitrate or nitrite considerably reduced its uptake. This explains an impaired effect with simultaneous intake of some vitamins and antioxidants. (113)

Likewise, the differences in metabolism of substances in animals as opposed to humans must always be considered. For example, rats and mice have the ability to independently generate ascorbic acid in the gastric tract. A higher concentration of ascorbic acid is relevant in this context in that it contributes to intestinally increased NO synthesis. -In other words, the substituted nitrate or nitrite is converted more efficiently in these animal organisms than is possible in humans, which in turn raises doubts as to whether the results from these animal studies can even be transferred to ourselves in this form. (113)

In any case, it is a fact that a positive vascular and antihypertensive effect under nitrate and nitrite substitution could also be demonstrated in humans, but not in the same highly effective form as this was shown in experiments with rats or mice. Whether an additional substitution with vitamin C (=ascorbic acid) could provide the results achieved in animal experiments remains to be seen due to still limited clinical data. (113)

6.2 The potential of the bitter melon

The fact that nutrition plays an essential role in the development of obesity, metabolic syndrome and ultimately T2DM also leads to the opposite approach: namely, that certain foods, primarily plant-based ingredients, may also have antidiabetic potential. In fact, this assumption has already been confirmed several times in experimental and clinical studies with various plants. Besides turmeric, soybean, ginger, pomegranate and the well-known medicinal plant aloe vera, the bitter melon (*Momordica charantia*) was particularly convincing due to its blood sugar lowering effect. (114)

Its ingredients charantin as well as vicin represent a possible starting point in the development of new pharmacological drugs for the prophylaxis of T2DM, as was proven in animal studies.

In a recent study with published results in April 2021, experiments were conducted on rats. One half of the rats collective got purposely fed high-caloric, high-sugar diets to induce hyperglycaemia and diabetes; the other half was allowed to maintain a normoglycaemic metabolic state to serve as a valid comparator of a healthy population.

Daily, the animals were fed various portions of bitter melon in addition to other accurately documented diets. The intake was divided into two different doses of 150 mg per kg body weight and 300 mg per kg body weight.

Differentiation of the two cohorts into further subgroups depending on exactly which part of the fruit was consumed showed that all parts of the fruit, but primarily the seeds contained the valuable hypoglycaemic ingredients. (115)

A reduction in blood glucose, glycosuria, and glomerular filtration rate results from several different mechanisms depending on the study. Decreased glucose uptake from the intestine(116,117), secretory effects on GLP-1(118), a reduction in gluconeogenesis, and glycolysis in the liver (119) are just a few of the recognized effects.

Moreover, already in 2017, the so-called mcIRBP-9 was identified as a protein of *Momordica charantia*, which binds to the insulin receptor at a different site than insulin and thus exerts a synergistic effect on insulin. Thus, an increased glucose uptake into the cells is achieved through the increased incorporation of GLUT-4. (120)

Most exciting, however, appears to be the fact that positive effects on ß-cells have already been attributed to bitter melon in several studies. Besides protective, even regenerative functions among others by an increase of the antioxidant superoxide dismutase, the number of ß-cells of the islets of Langerhans is thus surprisingly increased after its destruction or damage. (119)

The transcription factor PDX1 should be mentioned as another important mechanism of this phenomenon. This factor is essential in the correct development of the pancreas and a sufficient stimulation of the ß-cells. (120,121)

However, essential for the therapy or prevention of a T2DM is the benefit that comes along with the thus increased insulin secretion.

Whether these effects observed in animals can also be applied to humans in this form will have to be examined in more detail in future clinical randomized control studies. (115)

7 Results

As has been demonstrated several times, patients with hyperglycaemia are more likely to develop a severe case of COVID-19.

Not only the severity of the disease, but also the correspondingly more frequent severe consequences, such as the development of ARDS, the medical resources required as a result, such as intensive care beds, assisted mechanical ventilation or even tracheal intubation represent a problem.

Diabetics, with their diverse micro- as well as macrovascular damage, are particularly predisposed in this area, which is why this patient collective is also particularly susceptible to thromboembolic events in the context of such an infection.

Thus, appropriate management of elevated blood glucose levels appears even more important and significant. The multiple drug classes as already discussed and listed above are also used for proper glycaemic control in the setting of a SARS-CoV-2 infection.

The following table once more visualises results from multiple studies where the adverse outcome in patients suffering from COVID-19 and elevated blood glucose levels could be demonstrated.

Study type	Study origin	Study population	Prevalence of diabetes	Parameter	Outcome
Retrospective	China	810	100	Median blood glucose during hospital stay	↑ Mortality ↑ ARDS ↑ Cardiac injury ↑ Renal damage
Retrospective	Italy	59	42.4	Blood glucose at the time of hospital admission (>7.7 mmol/l)	↑ Disease severity ↑ Mortality ↓ Survival
Cohort	UK	17 278 392	9.9	HbA_{1c} (≥7.5%)	↑ Mortality
Retrospective	China	904	15	Hyperglycaemia	↑ Mortality
Retrospective	China	269	19.3	Hyperglycaemia	↑ Mortality
Retrospective	China	28	100	Random hyperglycaemia	↑ Disease severity ↑ ICU admissions ↑ ARDS ↑ Mortality
Retrospective	USA	1122	40.2	HbA_{1c} (≥6.5%) and uncontrolled hyperglycemia	↑ Mortality ↑ Median length of stay at hospital
Cohort	Kuwait, USA	417	23.3	Fasting blood glucose levels	↑ ICU admissions
Retrospective	China	166	36.7	Fasting blood glucose >7.0 mmol/l, but HbA_{1c} (<6.5%)	↑ ICU admissions ↑ Mechanical ventilation ↑ Mortality

Table 4: Hyperglycemia and COVID-19 Outcomes. Adapted from (29)

It should be noted, that in the study from which this table was derived and adapted, uncontrolled hyperglycaemia was defined as “more than two blood glucose measurements over or equal to 180 mg/dl within any 24 hour period”. (29)

Even though this table mainly presents data from China, because SARS-CoV-2 was primarily prevalent there, the aforementioned worse outcome in COVID-19-affected hyperglycaemic individuals is evident.

Whether or which drug classes have a better course and fewer long-term consequences is currently being elaborated in more detail. However, there is already evidence of a positive outcome for some individual classes or agents of oral antidiabetics compared to a treatment without the usage of these drugs.

Since metformin is considered the most common first-line drug, it has also been the subject of the most studies in connection with SARS-CoV-2 infections. It must be noted, however, that due to the relatively recent subject matter, long-term study results are of course not yet available, but only observations and potential explanations can be made.

For example, it can be deduced from the common mechanism of action of metformin that the suppression of the appetite results in weight reduction, which in turn leads to less adipokines being secreted by adipose tissue and therefore a reduction in overall inflammation. The positive effects on insulin resistance, improved glucose control and on the regulation of the immune system have also been observed. (94,95)

Another paper also discusses a protective effect of metformin related to a lower rate of viral infection.

This theory states, that via phosphorylation through the metformin activated AMPK-modulated signalling pathways the attachment to the main attack receptors of SARS-CoV-2, the ACE2 receptor, as well as the DPP4 receptor on T cells, is decreased.(29)

Therefore, less attachment site for the virus to invade the human body remains and this in return also leads to an improved immune response, which in a certain limited way also makes this drug antiviral.

In addition, metformin has a benefit on the vascular system, to be exact on the endothelium. Through lowering the oxidative stress and the endothelial inflammation a protective effect has been proven.(97, 98)

Furthermore, lower platelet aggregation has also been postulated to be associated with metformin use, which in turn would lead to less problematic thromboembolic events and a significant decrease in mortality.(95)

Another study even talks about the fact that an administration of metformin in the given scenario, i.e. in COVID-19 type 2 diabetics, is associated with a fourfold lower rate of in-hospital deaths, as opposed to non-users. (98)

However, what should be taken into account under all circumstances and at all times prior to the application of any medication, including the use of metformin, are any contraindications that may be present.

On top of various drug interactions, that also lead to a reduction in blood glucose, such as ß-blockers and corticosteroids, the serious effects of lactic acidosis should always be considered. Particular caution should be exercised in patients with impaired renal function, or more severe renal insufficiency detectable by the laboratory equivalent of a decreased glomerular filtration rate, among others.

It is therefore essential to determine the patient's individual concomitant diseases and to take into account any contraindications before using a drug in order not to cause the patient more harm than good.(99,100)

Still, in conclusion, the data on the benefits of antihyperglycemic therapy for type 2 diabetics have shown promising results, especially for metformin in the context of infection with SARS-CoV-2.

8 Discussion

Not only the high prevalence, but especially the globally rising incidence of T2DM in increasingly younger age groups should set alarm bells ringing all over the world. The significant long-term consequences of elevated sugar levels not only irreversibly damage multiple organ systems but also lead to generalized inflammatory reactions in the body. Due to these pre-damages and pathological processes in affected organisms, infection and illness with SARS-CoV-2 also lead to increased hospitalization rates and an increased risk of mortality.

Not least for this reason, early measures against obesity and subsequently, against the development of T2DM represent an integral part of health care and disease prevention. In addition to preventive measures such as regular exercise and a healthy, balanced diet, comprehensive education of the population should be the goal. Thanks to screening programs, an adequate, early diagnosis should be made possible for those affected, as well as individual evaluation for antihyperglycaemic therapy for blood glucose control.

Especially the control of the HbA_{1c} value and the indication of a medication-supported blood glucose control are essential in the prevention of various organic side effects, which can develop in the context of long-term existing hyperglycaemia.

These circumstances should also be of greatest interest to health care systems and health insurances of countries all over the world, as the global T2DM pandemic causes considerable additional costs and will devour even more financial resources with each additional person affected in the future.

This thesis addresses the question of whether certain oral antidiabetic agents offer a potential benefit, such as reduced mortality and/or improved outcome in patients with T2DM in the setting of COVID-19 disease.

Although the studies published to date have shown that a more favourable outcome was achieved with the use of some oral antidiabetic agents, the data available on this extremely recent topic are still relatively limited and often not statistically significant. As a result, there is not only a lack of long-term but also of international, broadly based studies with diverse and representative patient populations. Taking into account the data situation, this in return makes it hardly possible to derive generalized statements at the present time.

One substance, namely the first-line therapeutic metformin, certainly represented the primary area of interest for research in this context due to its frequent use. For this drug though, a reduced mortality during COVID-19 as well as further benefits could be proven throughout multiple studies.

There is also a constant risk of study bias due to confounding. In this context, especially due to the fact that type 2 diabetics have been prescribed different oral antidiabetic drugs depending on their individual needs.

Furthermore, a differentiation of the damage caused by hyperglycaemia in comparison to the damage caused after or during an infection with SARS-CoV-2 in pre-existing diabetics proves extremely difficult.

In summary, based on the current state of knowledge, a definitive antihyperglycaemic therapy for a better outcome of diabetics in the context of a novel coronavirus disease cannot be recommended due to a still lacking and partly even controversial data situation.

It therefore remains to wait for further studies not only on this topic, but also for future research results on potential new oral antidiabetic substance groups.

Perhaps, with increasing measures, it will be possible to get this pandemic within a pandemic under control in the coming years. Thus, the future in this field of research remains highly exciting and topical for the next generations as well.

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