End-organ damage in diabetes
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2015

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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General introduction
INTRODUCTION

Regulation of blood glucose levels is of paramount importance to human physiology. Normally, blood glucose level is tightly regulated as a part of metabolic homeostasis. When blood glucose falls below a certain level, the body starts to use stored sugar as an energy source through glycogenolysis, and converses stored glycogen in the liver and muscle to glucose, which can then be utilized as an energy source. Conversely, when blood glucose exceeds the normal level, the excess glucose (which otherwise would be toxic) is removed from the blood by the action of insulin, a peptide hormone produced by beta-cells of the pancreas. Key mechanisms dispatching the action of insulin consist of the promotion of the uptake of glucose in skeletal muscle and fat tissue and of shifting metabolism towards fat storage rather than fat utilization for energy.

When regulatory mechanisms fail to adequately maintain blood glucose within the normal range, conditions of abnormally diminished (hypoglycemia) or excessive (hyperglycemia) blood glucose levels occur producing a variety of symptoms. Hypoglycemic symptoms and manifestations are related to the actions produced by counter regulatory hormones (adrenaline and glucagon) triggered by the falling glucose level (e.g. shakiness, anxiety, tachycardia, sweating, hunger, nausea, headache, etc.), and the neuroglycopenic effects by the reduced brain glucose level (e.g. mental abnormalities and personality change, fatigue, weakness, blurred/double vision, lack of coordination, etc.). Brain effects can range from mild dysphoria to serious seizures and unconsciousness. In contrast, when temporary, hyperglycemia is often benign and asymptomatic. Blood glucose levels can rise well above normal for significant periods without producing any obvious effects or symptoms. However, chronic hyperglycemia at levels more than slightly above normal may produce a wide variety of serious complications over a period of years. When the glucose concentration in the blood remains high over time, the kidneys will reach a threshold of reabsorption, and glucose will be excreted in the urine (glycosuria). This increases the osmotic pressure of the urine and inhibits reabsorption of water by the kidney, resulting in increased urine production and increased fluid loss. The decrease in blood volume is compensated by water held in body cells and other body compartments, causing dehydration and thirst. Consequently, the classical symptoms of hyperglycemia, next to polyphagia, are polydipsia and polyuria.
Chronic hyperglycemia that persists even during fasting defines a state referred to as diabetes mellitus (DM). DM is due to insufficient production of insulin by the pancreas, or by insensitivity of body cells to the action of insulin. There are three main types of DM. (i) Type 1 diabetes mellitus (T1DM) results from the body's failure to produce sufficient amounts of insulin, the cause of which is unknown. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". (ii) Type 2 diabetes mellitus (T2DM) starts with a condition in which cells fail to respond to insulin properly, termed "insulin-resistance". As the disease progresses insufficient production of insulin may also develop due to beta cell exhaustion. This form was previously referred to as "non-insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes". (iii) Gestational diabetes is the third main form occurring in pregnant women, who develop increased levels of blood glucose without a previous history of diabetes. During pregnancy, the placenta, which connects baby to mother blood supply, produces high levels of various hormones which impair the action of insulin in the mother. Gestational diabetes usually develops during the second half of pregnancy.

**Trends in obesity, metabolic syndrome and T2DM leading to cardiovascular disease**

In 2011, according to International Diabetes Federation, an estimated 366 million people worldwide had diabetes, with type 2 making up the majority of the cases. Its prevalence is increasing rapidly and is estimated to be almost doubled by 2030 [1]. Diabetes occurs throughout the world, but is more common (especially type 2) in the more developed countries. However, the largest increase in prevalence is expected to occur in Africa, where the incidence is predicted to be amongst the highest by 2030 [2]. The increase in incidence in developing countries follows the trend of urbanization and lifestyle changes, perhaps most importantly a "Western-style" diet. This has suggested an environmental (i.e., dietary) effect although there is little understanding of the mechanism(s) at present. However, striking similarities have been observed between epidemic increases in overweight and obesity with the profound increases in DM in recent decades. Overweight goes hand in hand with the development of T2DM. People who are overweight are at much greater risk of developing T2DM than individuals with normal weight. In fact, obesity is at the background of the risk of developing T2DM [3].
It is well known that obesity commonly coexist with insulin resistance, although causal links between insulin resistance, obesity, and dietary factors are complex and controversial [3]. It is possible that one of them arises first, and tends to cause the other; or that insulin resistance and excess body weight might arise independently as a consequence of a third factor, but end up reinforcing each other. Some population groups might be genetically predisposed to one or the other. Central obesity is the principal symptom of what is referred to as "metabolic syndrome" (MetS), a disorder of energy utilization and storage also known as (metabolic) syndrome X, cardiometabolic syndrome and Reaven's syndrome, amongst others. MetS is diagnosed by a co-occurrence of three out of five of the following medical conditions: abdominal (central) obesity, elevated blood pressure, elevated fasting plasma glucose, high serum triglycerides, and low high-density cholesterol (HDL) levels [4]. Risk factors of MetS include, but may not be restricted to, stress, overweight and obesity, sedentary lifestyle, Western dietary pattern, hyperphagia and ageing.

Crucially, however, MetS markedly increases the risk of developing DM and cardiovascular disease (CVD). MetS and DM are associated with dyslipidemia which is also a risk factor for CVD. Dyslipidemia is associated with impaired carotid artery elasticity, intima-media thickness and brachial flow-mediated dilatation [5]. Atherosclerotic plaque is associated with the elevation of non-high density lipoprotein cholesterol [6]. As dyslipidemia develops the number of risk factors and severity of asymptomatic coronary and aortic atherosclerosis increases. In addition, DM itself is suggested to be an inflammatory disease and important risk factor for CVD as statistics indicate a strong correlation between CVD and DM. Hence, adults with DM are more likely to have heart disease or stroke than adults without DM [7]. Heart diseases and stroke actually are the number 1 causes of death and disability among people with T2DM. In fact, a considerable percentage of people with DM do not die of DM itself but of some form of hypertension, heart disease or stroke! [7]. As highlighted later on in this thesis, we believe that this importantly involves the effect of DM attenuating vascular function.

The diabetes epidemic is an epidemic of diabetic micro- and macrovascular complications
In the United States alone, nearly 174 million people have undiagnosed DM, as delineated from over 744 reviewed data sources [8], but at the same time are at great risk to develop end-organ damage and die from CVD. There is consensus that key to the increased mortality are the changes in micro- and microvasculature.

Atherosclerosis is a main consequence of macrovascular disease in DM. Narrowing and stiffing of arterial walls throughout the body - which is formed by the build-up of fats, cholesterol and other substances in and on the arteries walls (plaques) - can restrict blood flow. These plaques may burst and trigger the formation of blood clots and heart problems [9,10].

People with DM may experience damage to micro vessels and nerves, e.g. in the back of the eye leading to diabetic retinopathy, a condition of eye problems that may include reduced vision [11]. Indeed, DM is the main cause of acquired blindness in people under the age of 65 and is one of the leading causes in older adults. DM may also cause damage to micro vessels in the kidney leading to diabetic nephropathy and the attenuation of kidney structure and function. This can progress to a devastating disease: kidney failure. Treatment of kidney failure requires dialysis or transplantation. These procedures are a burden to patients and society. Hence, DM is the main reason for Americans to be dialyzed. Furthermore, chronic kidney disease per se is a risk factor for CVD thereby further contributing to the high incidence of cardiovascular mortality in DM [12,13].

Diabetes also may damage the peripheral nervous system innervating the arms and legs. Affected patients experience pain, and tingling or buzzing sensations in their hands and/or feet. Patients may lose bladder control, or the ability to walk, and males show loss of ability to function sexually (impotence or erectile dysfunction) [14]. Other complications of DM include diabetic dermopathy and cognitive disturbances. Nevertheless, the majority of DM patients develop micro- and macrovascular disease and die from CVD.
Figure 1. By increasing metabolic syndrome and diabetic mellitus, the complications of micro- and macrovascular dysfunction and end-organ damage raises significantly.

Prevention and treatment of diabetes: current measures and limitations

The above may be summarized in a scheme of conditions in which micro- and macrovascular disease associated with or resulting from DM leads to development of end-organ damage and death from CVD: see Figure 1. Of note in this scheme are the initial conditions in MetS which precede and feed the development of DM, and the notion that initial overweight/obesity at the start of the scheme currently is a growing global issue reaching epidemic proportions. The consequence hereof is a threatening revival of premature CVD-morbidity and -mortality worldwide, and an associated rise in economic (health care) costs. The current diabetes treatments indeed improved general complications
but still not enough to halted and reversed the complications of CVD-events. Hence, to improve diabetes outcome nowadays necessitates both the prevention of (epidemic) DM2 and development of adequate strategies coping with its consequences.

The main measure to prevent development of DM consists of life-style changing measures to prevent initial conditions (of MetS) leading hereto (Figure 2). These consist of changing a diabetic prone lifestyle such as decreased physical activity and replacing the ‘Western type diet’ of high fat food, refined sugar and excessive processed red meat with a high fiber and green diet. In addition, proper pharmacological treatments are needed to control the condition of per se DM and its consequences: the anti-diabetic drugs (Figure 2). Current pharmacological interventions that have been developed in recent years are aimed at controlling plasma glucose levels either by inhibition of gluconeogenesis or increasing the levels of insulin or improving the body's sensitivity to insulin. Nowadays a range of anti-diabetic medicines are clinically available, including insulin, sulfonylureas, disaccharidase inhibitors, thiazolidinediones, meglitinides, GLP analogs, amylin analogs and DPP-IV inhibitors which can be used alone or in combination of together [15].

Unfortunately, the effectiveness of lifestyle changes to prevent DM are not always successful. This may be due both to poor compliance but also a lack of knowledge regarding specific gene-environment interactions that predispose to DM. Hence, we do not always know which individuals are more at risk of developing DM as compared to others, meaning that "standard" lifestyle changing programs may "work" for some in the general population but not all. Such programs could be more successful when focused on (groups of) individuals who are more likely (i.e. at risk) to enter the obesity-MetS-DM sequel or suffer its consequences to a higher extent (i.e. a higher degree of mirco- and macrovascular disease and end-organ damage than others). Such (groups of) individuals could be more specifically targeted at an earlier stage, were it not that these individuals are insufficiently identified at present.

In a similar way, not all of the currently available anti-diabetic drugs actually are successful in all DM patients. Some anti-diabetic drugs seem to provide less CVD-benefit than would be expected based on their ability for glycemic control. Vice versa, other treatments seem to provide protection against end-organ damage in DM that goes beyond glycemic control, but via mechanisms and targets which are largely unknown.
Figure 2. Current measures to prevent diabetes include a change in sedentary life-style and dietary patterns next to the anti-diabetic treatments that aim to control hyperglycemia.

**A chance for innovative targets and therapies**

Thus besides (1) preventing diabetes and (2) treating its symptoms, discomforts and life-threats directly associated with hyperglycemia as in current approaches, additional important goals include (3) a better identification of (groups of) individuals who are at higher risk of developing DM or more severely suffering its consequences and (4) the *per se* prevention of end-organ damage in DM.

(ad.3) Individual susceptibility to end-organ damage is largely variable anyhow, even among seemingly similar (normal healthy) individuals. The possibility to identify those
individuals who are at a risk of developing a higher degree of end-organ damage when DM develops would provide additional options for 'personalized medicine' at an early stage. Variability in vascular function among subjects at apparent normal health could be such an identifier of an individual's susceptibility to end-organ damage but this has not yet been studied in subjects prone to develop MetS and DM. If so, however, vascular function would be an important pharmacological target, both in pre-DM (i.e. to reduce initial susceptibility to end-organ damage in DM) and in DM-conditions (i.e. to inhibit the progression of existing end-organ damage).

(ad.4) The per se prevention of end-organ damage in DM further implies that a potential direct protective (i.e. pleiotropic) effect of an anti-diabetic compound against end-organ damage is as relevant as its property (by definition) to control hyperglycemia. Such effects may include actions on yet unidentified targets but which bear significant relevance to end-organ damage in DM. Taken together, the above provides relevant opportunities for innovative new targets and therapies, as summarized in Figure 3.
Figure 3. Maintaining the integrity of vascular function can be considered an important target for MetS and DM treatment.

**Targets and treatments explored in this thesis**

The aim of this thesis was to explore new targets and therapies to prevent end-organ damage in diabetes. To this end we focused on:

1. vascular function as a predictor of individual susceptibility to end-organ damage in subjects prone to developing DM,
2. key mechanisms of end-organ damage in DM as potential new targets of therapy,
3. pleiotropic vascular/hemodynamic effects of existing anti-diabetic agents and promising non anti-diabetic agents.
Ad.1 To address the above we first employed the obese Zucker diabetic fatty rat (ZDF) model of end-organ injury and function loss in DM in Chapters 2 and 3. In **Chapter 2** the aim was to study the predictive value of intra-organ vessel function for an (normal?) individual's susceptibility to develop end-organ damage in DM. To this end, intra-renal vascular function was assessed in young ZDF when still at pre-diabetic state and without renal damage. Individuals were then followed over time for urinary protein excretion and glomerulosclerosis as indices of renal injury during DM development, and correlated this with intra-renal artery function at baseline.

Ad.2 The ZDF model was also used for the studies of brain damage in DM. Protein aggregate formation is a common feature of neurodegenerative diseases leading to neurofibrillary tangle formation with cognitive deficits. In **Chapter 3**, we studied the presence of protein aggregation in the frontal brain of ZDF with aim to identify key mechanistic targets. Given their roles in proteostasis and brain anti-oxidant formation, respectively, we focused on the mTOR-pathway and H2S producing enzyme cystathionine beta synthase (CBS).

Ad.3 Endothelial dysfunction has emerged as a target for primary prevention strategies in CVD. It has been suggested that certain anti-diabetic drugs - e.g. metformin - provide cardiovascular benefit beyond glycemia control, possibly via a (glucose-independent) direct effect on vascular function. In **Chapter 4** we used spontaneously hypertensive rats (SHR) - a model of endothelial dysfunction in a setting of HT - to further investigate this. Endothelium-dependent relaxation was studied in aortas of SHR with and without streptozotocin-induced type 1 DM (T1DM) after long-term treatment with metformin or vildagliptin. Finally in **Chapter 5** we studied the vascular treatment effects of FTY720 (fingolimod). Interest in this novel immunomodulator for treatment of T1DM has increased recently. FTY720 suppresses the immune response by sequestering circulating mature lymphocytes from the blood and peripheral tissues to secondary lymphoid tissues and the thymus. It has been suggested that similar mechanisms may help to protect islet beta cells from autoimmune destruction at an early stage of DM. First results in animal studies are promising but whether this might involve potential effects of FTY720 via modulation of vascular S1P receptor function is unknown.
Chapter 1

References


