Second Edition

Student's guide to Diabetes

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Preface.

This review is primarily intended as an aid for students of biology or medicine interested in achieving an overview of diabetes mellitus, including its history, classifications, types, prevalences, complications, treatments, present research directions, various animal models of diabetes, and today's perception of diabetes.

Diabetes is the collective name for a group of diseases resulting in persistent hyperglycaemia, and unless this symptom is treated either medically, surgically, by adjusting the diet, increasing the physical activity, or a combination, every organ in the body can be damaged. The end result is a drastic reduction in life expectancy and the last few months or years will in all likelihood be no bed of roses. However, treatment of symptoms should not be confused with a cure and even the best-treated patients do experience an increased risk of long-term complications.

Since maybe a fifth of the world's population is presently estimated to be suffering from some kind of diabetes (including "*pre-diabetes*"), it is clear that these diseases are taking a heavy toll on both patients and societies in terms of personal sufferings, medical treatment expenses, sick leave, lost productivity, etc. The costs of diabetes were estimated to be around 465 billion USD globally in 2011 [1] which almost matches the total budget of NASA between 1959 and 2015 (486 billion in 2010-dollars), including funding of the entire Apollo programme and development and maintenance of the space shuttles as well as the International Space Station [2].

However, besides being a significant source of suffering for both patients and state budgets, diabetes is also a significant source of revenues. The global market of diabetes alone maintained an annual growth rate of just below 20% in the period 1995-2005, ending at 17.8 billion USD, and was at the time (2006) expected to continue as "*one of the most attractive growth areas of the global pharmaceutical market*" [3]. The reasons are mainly that the prevalence of diabetics is steadily increasing; that the treatment of the symptoms has become more aggressive (increased glycaemic control and often more than one simultaneous treatment per patient), and the use of new generations of treatments which typically are more expensive than previous generations [3]. A more recent (2012) report estimates that the global diabetes diagnostics market alone will reach 32 billion USD by 2017 [4].

In short, one man's scourge of modern times is another man's big business, and this diabetes epidemic evidently *also* presents immense opportunities for many parties. It is consequently important for both students and professionals within the fields of diabetes to remain critical toward information, particularly when served by the most obvious stakeholders (companies, diabetes-related organisations, researchers requiring continued funds for their projects), and not take too much for granted.

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What you are about to read now is more or less a direct copy of the introduction to diabetes I presented in my recently defended PhD dissertation [5]. When I started to look into these diseases I found it somewhat frustrating that it was so difficult to obtain a decent understanding because the usual diabetes-related organisations seemed mostly concerned with presenting new alarming epidemiological data and because scientific reviews and scientific papers were usually focused on just one aspect. I also turned to diabetes-related PhD dissertations, hoping that they would at least be a little better to "get around" the basics, but I was not that impressed so I tried to use common textbooks instead. However, although they would indeed explain some simple characteristics practically never mentioned in reviews and papers, they were typically also somewhat superficial and difficult to obtain.

It eventually seemed to me as if many of these so often repeated headlines in relation to diabetes were in fact bordering the misleading, so in the end I decided to start from scratch and make exactly the type of review that I would personally have appreciated being able to read before I started my own research. The result was, admittedly, a total "overkill" but the upside is that you can now use this review as a compact guide to these diseases.

This second edition of *Student's guide to Diabetes* only adds minor revisions to the first edition. I hope you will enjoy the reading and that you will afterwards also feel you have achieved a better understanding of the "grand picture" in relation to diabetes.

Bryan Schønecker.

Hareskovby, Denmark, April 2014.

Abbreviations.

ADA	The American Diabetes Association.
AG	Average blood glucose.
AGEs	Advanced glycation end-products.
BB-DP	BioBreeding diabetes-prone rats.
BB-DR	BioBreeding diabetes-resistant rats.
CNS	Central nervous system.
FPG	Fasting plasma glucose.
GAD65	Glutamic acid decarboxylase 65 (molecular weight 65 kDa).
GAD65a	GAD65 autoantibodies.
GDM	Gestational diabetes mellitus.
GIP	Gastric inhibitory polypeptide.
GLP-1	Glucagon-like peptide-1.
HbA_{1c}	Glycosylated hemoglobin A1c.
HLA	Human leukocyte antigen.
HPA	Hypothalamic-pituitary-adrenal.
IAA	Insulin autoantibodies.
IA-2	Tyrosine phosphatase protein ICA512.
IA-2A	Antibodies against IA-2.
ICA	Islet cell autoantibody.
IDDM	Insulin dependent diabetes mellitus.
IDF	The International Diabetes Federation.
IFG	Impaired fasting glucose.
IGT	Impaired glucose tolerance.
KDP	Komeda diabetes-prone rat.
LADA	Latent autoimmune diabetes of the adults.
LETL	Long-Evans Tokushima lean rat.
LEW	LEW.1AR1/Ztm-iddm rat.
MHC	Major histocompatibility complex.
MODY	Maturity onset diabetes of the young.
NIDDM	Non-insulin dependent diabetes mellitus.
NOD	Non-obese diabetic mouse.
OGTT	Oral glucose tolerance test.
T1D & T2D	Type 1 diabetes & Type 2 diabetes.
WHO	World health organization.

Chapter 1 - Fundamentals of untreated diabetes mellitus.

For the average person living in e.g. Denmark, untreated diabetes generally means that the symptoms have not progressed enough to persuade the affected person to consult the local physician and commence treatment. In other parts of the world, however, a considerable fraction of low-income diabetics will experience first-hand how an untreated diabetes can progress. The global number of starving people was estimated to reach 1.02 billion in 2009 [6] and starving people cannot, of course, afford to pay for proper diabetes treatment. Even in places where insulin is subsidized and *theoretically* within the financial reach of the individual diabetic patient, other factors such as huge travel distances to care units and scarcity of properly trained health care staff will prevent many diabetics from being diagnosed, or for that matter, treated accordingly thereafter [7-9].

To fully appreciate the seriousness of diabetes it is necessary to know its natural history, so in order to provide such an overview I have distilled the rest of this chapter from references [10-17], unless otherwise indicated.

Untreated diabetes is characterised by diminished levels and/or reduced effect of the pancreatic hormone insulin and the resultant presence of chronic hyperglycaemia (casual blood glucose levels above 11.1 mM [18]). Briefly stated, the beta cells in the pancreatic islets of Langerhans respond to the actual level of blood glucose and release insulin when the level is high and reduce secretion when the level is low. Insulin increase glucose uptake in most of the tissue and trigger enzymatic cascades that subsequently synthesize fatty acids and triglycerides in the liver/adipose tissue, convert glucose to glycogen in the liver/muscles and synthesize protein in most tissue. Insulin simultaneously counteracts the catabolism of the same macromolecules and, worth noting, inhibits the release of glucose from the liver.

The islets of Langerhans also contain glucagon-producing alpha cells. Glucagon antagonises the effect of insulin and is released following stimulation from the sympathetic nervous system and adrenaline (also known as “epinephrine”, and part of the “stress-response”) and if the level of glucose in the blood is low. Glucagon possibly inhibits the secretion of insulin, too, and is an extremely potent

hyperglycaemic agent (one molecule can cause the release of approx. 100 million molecules of glucose). The main target of glucagon is the liver where it stimulates glycogenolysis (glycogen => glucose), gluconeogenesis (synthesis of glucose from lactate and other molecules), and the release of glucose from the liver to the blood. Glucagon also stimulates the breakdown of proteins and lipids in other cells as well as the synthesis of ketones (also known as ketone bodies).

In persons with abnormal low levels of insulin, e.g. as in type 1 diabetes (T1D), glucose clearance from the blood is decreased since the only organs and tissues that do *not* require insulin to facilitate the transport of glucose over the cell membrane is the liver, kidney, exercising skeletal muscles, and neural tissue. Lack of insulin-facilitated transport of glucose in other tissues will itself lead to hyperglycaemia but the major reason for the resultant and severe hyperglycaemia is the increased release of glucose from the liver due to abnormally high levels of glucagon.

Hypersecretion of insulin can be the result of a pancreatic cancer but the usual reason, as seen in type 2 diabetes (T2D), is that the beta cells compensate for the reduced sensitivity towards insulin in the major target cells (liver, adipose tissue, resting skeletal muscles). Eventually the condition can progress to a point where the transfer of glucose over the cell membranes is severely impaired, resulting in increased levels of glucose in the blood. High levels of insulin and glucose would normally result in low secretion of glucagon and thus inhibit liver outlet of glucose but since the glucose permeability in the alpha cells depends on insulin, too, glucagon levels can be abnormal high in both types of diabetes. In such cases the liver is stimulated by the glucagon to increase its outlet of glucose and if the liver also have reduced sensitivity towards insulin, the normal inhibition from insulin will be diminished. The end result is a severe hyperglycaemic state.

When the cells in the body do not have the same easy access to glucose to fuel their metabolism, they will increase their dependency on protein and fat. As result, fat and proteins are mobilized at a higher than usual rate leading to the presence of high levels of amino acids and fatty acids (lipemia, also known as lipidemia) in the blood. Fatty acids are weak acids, as are their ketone metabolites, one of which (*acetone*) is easily detectable by a human nose in the exhalations of a severely ill and untreated diabetic.

Increased levels of ketones in the blood (ketosis) can affect blood pH. If the pH is lowered (as in the case of ketoacidosis) relative to the normal narrow interval (pH 7.38-7.42) by just a few tenths of a unit, the central nervous system can be depressed as can the heart activity and oxygen transport. The brain can operate for long without insulin, but as the pH decreases further, the patient will start to feel dizzy, lethargic and eventually slip into a coma, which can be fatal since pH values below 6.8 for even a few seconds will result in immediate death. Lowering of the blood pH by excess ketones will drive the equilibrium between carbonic acid and bicarbonate (i.e. the blood buffer system) towards a build-up of carbonic acid to which the respiratory system react by the so-called Kussmaul's respiration. The breathing is at first rapid and shallow but gradually becomes more deep, slow and laboured as the acidosis progresses and in the process carbonic acid is exchanged over the lungs as CO_2 and water.

A state of hyperglycaemia will transgress the renal threshold (approx. 10 mM in humans) so the kidneys are no longer capable of withholding the glucose which is now excreted in the urine (glucosuria). Glucose acts as an osmotic diuretic so it will lead to vast quantities of water in the urine outlet (polyuria), leading to *dehydration* (clinical indication is soft eyeballs in the patient) which together with the caloric losses (up to 100 g glucose lost/day) will trigger an increased impulse to drink excessively (polydipsia). Ketone bodies also begin to excrete during ketosis (ketonuria) and since ketones carry negative charges, they will attract positive charged ions such as Na^+ and K^+, which also will be lost in the urine.

A side effect of excessive hyperglycaemia and the serious electrolyte losses is a feeling of abdominal pains and nauseation which, incidentally, trigger the stress-response and stimulates the hypothalamic-pituitary-adrenal (HPA) axis to release glucocorticoids. The most important substance in this aspect (cortisol) will contribute to a further increase in blood levels of glucose, fatty acids, and amino acids. As a result of these changes, severe and untreated diabetes will affect the overall metabolism and imply increasing weight loss, muscle weakness, neuromuscular problems, poor ability to heal wounds, and circulatory collapse. After 1-2 years of "*exquisite anguish*" [19], death will typically follow an episode of ketoacidosis-induced coma.

Chapter 2 - Historical perspective on diabetes.

Diabetes is one of the earliest clinical syndromes recognised in the history of mankind and the concept has evolved from the initial inclusion of patients suffering from sweet tasting urine (glucosuria) and lesser symptoms over patients with increased levels of blood glucose (hyperglycaemia) to large groups of otherwise asymptomatic persons transgressing arbitrary blood glucose norms [20].

Already Indian texts from the 5th century BC described an illness…

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End of free sample.