MolCare Consulting | Dr. Bernd Becker | Schulsiedlung 6 | D-93109 Wiesent | Mobil: +49 173 66 79 505 - Tel: +49 9482 9099 036 - Fax: +49 9482 9099 037 - E-Mail: becker@molcare-consulting.com

Gut-Diabetes Connection

Gut microbiota in Diabetes

Diabetes mellitus

Diabetes mellitus (DM), commonly referred to as diabetes, is a group of metabolic disorders in which there are high blood sugar levels over a prolonged period. Diabetes is due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced. [1]. There are two main types of diabetes mellitus.

- **Type 1 Diabetes mellitus (Type 1 DM)** results from the pancreas's failure to produce enough insulin [2]. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes." The cause is unknown. [2]. Since in type 1 DM not enough insulin is produced, it is resulting in high blood sugar levels in the body.[2].
- **Type 2 Diabetes mellitus (Type 2 DM)** begins with insulin resistance, a condition in which cells fail to respond to insulin properly [2]. As the disease progresses a lack of insulin may also lead to progressive deterioration in b-cell function coupled with the addition of acquired insulin resistance for which the b-cell cannot compensate [3]. This form was previously referred to as "non insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes" [2].

Box 3.4 Clinical features of type 1 and type 2 diabetes

Type 1 diabetes	Type 2 diabetes
• Sudden onset with severe symptoms of thirst and ketoacidosis (vomiting, hyperventilation, dehydration)	• Usually insidious onset of tiredness, thirst, polyuria, nocturia
• Recent, marked weight loss. Usually lean	• No ketoacidosis
• Spontaneous ketosis	• Usually overweight or obese; often no recent weight loss
• Life-threatening; needs urgent insulin replacement	• Frequent infections, e.g. urine, skin, chest
• Absent C-peptide	• Symptoms may be minimal and/or ignored by patient
• Markers of autoimmunity present (e.g. islet cell antibodies)	• Often other features of 'metabolic syndrome', e.g. hypertension
	• C-peptide detectable

Table 1: Diabetes type info box [4]

1) Pathogenesis of Type 1 DM

Type 1 DM is a multifactorial disease in which genetic and environmental factors play a key role. The triggering event is still obscure, and so are many of the immune events that follow. Type 1 DM is primarily caused by the destruction of insulin producing beta cells. Cytotoxic T-lymphocytes execute the killing of insulin-producing beta cells during onset of type 1 DM [5].

One monogenic subtype of diabetes, **M**aturity **O**nset **D**iabetes of the **Y**oung (MODY) is characterized by young onset (usually before the age of 25 years) non-insulin dependent diabetes caused by b-cell dysfunction, with an autosomal dominant inheritance [6].

As with autoimmune diabetes, however, there is clear loss of b-cell function. Diabetes occurring before the age of 6 months is most likely to be monogenic neonatal diabetes rather than autoimmune T1DM [3, 6]. In addition to the typically young people with acute – onset T1DM, there is an older group with slower onset disease. They may present in middle age with apparent T2DM but have evidence of autoimmunity. This is referred to as latent autoimmune diabetes of adults (LADA) [3, 7].

2) Pathogenesis of Type 2 DM [8].

The pathological sequence for type 2 diabetes is complex and entails many different elements. For the development of a T2DM a genetic predisposition must exist. Type 2 DM is a heterogeneous disorder caused by a combination of genetic and environmental factors which adversely affect b- cell function and tissue insulin sensitivity. Type 2 DM develops because of a progressive deterioration in b-cell function coupled with the addition of acquired insulin resistance for which the b- cell cannot compensate. [3].

3) Regulation of Insulin Synthesis and Secretion and Pancreatic Beta-Cell Dysfunction in Diabetes [9].

Pancreatic ?-cell dysfunction plays an important role in the pathogenesis of both type 1 and type 2 diabetes. Insulin, which is produced in ?-cells, is a critical regulator of metabolism. The ?-cell is a metabolic hub in the body, connecting nutrient metabolism and the endocrine system. Thus, the b-cells are equipped with mechanisms to detect changes in circulating nutrients, in hormone levels, and in the activity of the autonomic nervous system [3, 9, 10]

In b-cells Insulin is synthesized as proinsulin. After processing of the proform in the vesicles of the golgi apparatus yielding insulin, it is stored in secretory vesicles. Insulin is released from the secretory vesicles by exocytosis. A process in which the granule membrane of the secretory vesicle and plasma membrane fuse together, releasing the vesicular contents into the interstitial space.

Release of insulin

When the glucose concentration outside the cell is high, Metabolism of the glucose produces ATP, which increases the ATP to ADP ratio [11]. This change in potential difference opens the voltage-gated calcium channels, which allows calcium ions from outside the cell to diffuse in down their concentration gradient. When the calcium ions enter the cell, they cause vesicles containing insulin to move to, and fuse with, the cell surface membrane, releasing insulin by exocytosis [12].

Diabetes and the Gastrointestinal Tract

Many gastrointestinal complications of diabetes seem to be related to dysfunction of the neurons supplying the enteric nervous system. involvement of the intestinal nerves may lead to enteric neuropathy. Inflammatory neuropathy of the enteric nervous system is one of symptoms associated with diabetes mellitus [13].

The Colon in Diabetes

Diabetes mellitus is a group of diseases with different types producing very similar symptoms with acute and chronic complications. Amongst these, gastrointestinal dysmotility, associated with the development of neuropathy in the enteric nervous system (ENS). The ENS shares embryological, morphological, neurochemical, and functional features with the CNS [14, 15]. The close homology between these two connected neural systems is strengthened by instances in which CNS disorders involve enteric neural dysfunction. For example, patients with Alzheimer’s or Parkinson’s diseases often manifest symptoms suggestive of disturbed bowel transit, including either diarrhea or constipation, which are likely due to underlying ENS dysfunction [14].

Probiotics and intestinal neuroimmunology

The human gastrointestinal tract contains a large and complex neural network called the enteric nervous system, whose main purpose is to regulate the physiological function of the gut and to modulate communication between the gut and the central nervous system. [16].Unsaturated fatty acids from plant and fish diets are enriched in ??3 fatty acids regulate the immune reactivity [17]. **Probiotics** are defined

as microorganisms that are believed to provide health benefits when consumed [18, 19]. Probiotics possess well documented decay properties in the prevention and treatment of diarrhoeal diseases [20, 21] as well as modulating immune responses [22].

The Gut flora, **gut microbiota** or **gastrointestinal microbiota** are a complex community of microorganisms providing a barrier to pathogenic organisms [23, 24]. The gut -associated lymphoid tissue (GALT), forms part of the intestinal epithelium and detects and reacts to pathogens appearing and developing during the time that the gut flora develops and establishes [24]. Even more, if the gut flora is disturbed and not homeostasis, can provoke auto immune diseases like rheumatoid arthritis, diabetes and multiple sclerosis [25].

Library

1. Shoback by gardner, D.G., ed. *Greenspan's basic & clinical endocrinology* 9th Edition ed. 2011, McGraw-Hill Medical: Nea York.
2. WHO, *Diabetes Fact sheet N°312*. 2013, who.
3. Holt, R.I.G., et al., eds. *Textbook of Diabetes*. 4th Edition ed. 2010, Blackwell Publishing LTD: Southern Gate, Chichester, West Sussex UK.
4. Bilous , R. and R. Donnelly, *Handbook of Diabetes*. 4th ed. 2010, Blackell publishing London: John Wiley & Sons Ltd.
5. Christoffersson, G. and M.G. von Herrath, *A Deeper Look into Type 1 Diabetes - Imaging Immune Responses during Onset of Disease*. Front Immunol, 2016. **7**: p. 313.
6. Pearson, E.R., et al., *Genetic cause of hyperglycaemia and response to treatment in diabetes.* Lancet, 2003. **362**(9392): p. 1275-81.
7. Tuomi, T., et al., *Antibodies to glutamic acid decarboxylase reveal latent autoimmune diabetes mellitus in adults with a non-insulin-dependent onset of disease.* Diabetes, 1993. **42**(2): p. 359-62.
8. Leahy, J.L., *Pathogenesis of type 2 diabetes mellitus.* Arch Med Res, 2005. **36**(3): p. 197-209.
9. Fu, Z., E.R. Gilbert, and D. Liu, *Regulation of insulin synthesis and secretion and pancreatic Beta-cell dysfunction in diabetes.* Curr Diabetes Rev, 2013. **9**(1): p. 25-53.
10. Weiss, M., D.F. Steiner, and L.H. Philipson, *Insulin Biosynthesis, Secretion, Structure, and Structure-Activity Relationships*, in *Endotext*, L.J. De Groot, et al., Editors. 2000: South Dartmouth (MA).
11. Santulli, G., et al., *Calcium release channel RyR2 regulates insulin release and glucose homeostasis.* J Clin Invest, 2015. **125**(11): p. 4316.
12. Lang, V. and P.E. Light, *The molecular mechanisms and pharmacotherapy of ATP-sensitive potassium channel gene mutations underlying neonatal diabetes.* Pharmgenomics Pers Med, 2010. **3**: p. 145-61.
13. Uranga-Ocio, J.A., et al., *Enteric neuropathy associated to diabetes mellitus.* Rev Esp Enferm Dig, 2015. **107**(6): p. 366-73.
14. De Giorgio, R., et al., *Inflammatory neuropathies of the enteric nervous system.* Gastroenterology, 2004. **126**(7): p. 1872-83.
15. Furness, J.B., ed. *The Enteric Nervous System*. 2006, Blackwell Publishing, Inc.: Oxford, UK.
16. Sharma, A., et al., *New technologies to investigate the brain-gut axis.* World J Gastroenterol, 2009. **15**(2): p. 182-91.
17. Swank, R.L., et al., *Multiple sclerosis in rural Norway its geographic and occupational incidence in relation to nutrition.* N Engl J Med, 1952. **246**(19): p. 722-8.

18. Hill, C., et al., *Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic.* Nat Rev Gastroenterol Hepatol, 2014. **11**(8): p. 506-14.
19. Rijkers, G.T., et al., *Health benefits and health claims of probiotics: bridging science and marketing.* Br J Nutr, 2011. **106**(9): p. 1291-6.
20. Isolauri, E.-., et al., *A Human Lactobacillus Strain (Lactobacillus Casei sp strain GG) Promotes Recovery From Acute Diarrhea in Children.* Pediatrics, 1991. **88**(1).
21. Saavedra, J.M., et al., *Feeding of Bifidobacterium bifidum and Streptococcus thermophilus to infants in hospital for prevention of diarrhoea and shedding of rotavirus.* Lancet, 1994. **344** (8929): p. 1046-9.
22. Ouwehand, A.C., et al., *Probiotics: mechanisms and established e!ects.* International Dairy Journal, 1999. **9**(1): p. 43 - 52.
23. Faderl, M., et al., *Keeping bugs in check: The mucus layer as a critical component in maintaining intestinal homeostasis.* IUBMB Life, 2015. **67**(4): p. 275-85.
24. Sommer, F. and F. Backhed, *The gut microbiota--masters of host development and physiology.* Nat Rev Microbiol, 2013. **11**(4): p. 227-38.
25. Shen, S. and C.H. Wong, *Bugging inflammation: role of the gut microbiota.* Clin Transl Immunology, 2016. **5**(4): p. e72.