© **2015** ILEX PUBLISHING HOUSE, Bucharest, Roumania
http://www.jrdiabet.ro
Rom J Diabetes Nutr Metab Dis. **22**(3):225-230
doi: 10.1515/rjdnmd-2015-0027

Editorial

PATHOPHYSIOLOGY OF TYPE 2 DIABETES: THE LONG JOURNEY INTO PRESENT

Bogdan-Mircea Mihai [1,2], ***Cristina Mihaela Lăcătuşu*** [1,2,✉], ***Elena-Daniela Grigorescu*** [2], ***Gina Eosefina Botnariu*** [1,2]

[1] University of Medicine and Pharmacy "Grigore T. Popa" – Iaşi, Romania
Faculty of Medicine
[2] Clinical Centre of Diabetes, Nutrition and Metabolic Diseases Iaşi, Romania

received: August 31, 2015 *accepted*: September 05, 2015
available online: September 15, 2015

Motto:
"The past is the present, isn't it? It's the future too."
Eugene O'Neill, *Long Day's Journey into Night*

Evolution and progress are the law of all things. All sciences, including medicine, have met an unprecedented development in the last years, and progress is obvious in all fields of medicine, including the pathophysiology of diseases. For instance, type 2 diabetes mellitus (T2D) was considered during the 90's to be determined by two essential pathophysiological processes, insulin resistance and β-cell deficiency. Knowledge at that moment was summarized in 1988 by Ralph De Fronzo within a now classical paper in *Diabetes*, where he spoke about a triumvirate that included the β-cell, the muscle and the liver, leading to the appearance and progression of T2D [1]. As the years passed by, medical science progressed and other processes, organs or substances were described as being involved in the pathophysiology of T2D, beside those previously accepted. Two decades later, it was once more De Fronzo who approached the subject, but speaking this time about an "ominous octet" [2]: liver and muscle insulin resistance, β-cell deficiency, abnormal adipocyte metabolism, reduced incretin effect, increased glucagon secretion, abnormal kidney reabsorption of glucose and neurotransmitters dysfunction in the central nervous system. This publication also became one of the most quoted papers in diabetology. Noteworthy, other authors approach the topic of T2D pathophysiology by emphasizing some aspects De Fronzo addressed only marginally, such as genetic factors (given the high heritability of the disease), early-life environment (fetal and neonatal programming and epigenetic effects) and the usual environmental factors. Therefore, at this moment it is an interesting concept to look upon T2D as a

✉ 1st Independenței Blvd., 700111, Iași, Romania, Telephone: +40723211116
corresponding author e-mail: cristina.lacatusu@umfiasi.ro / cmlacatusu@yahoo.co.uk

disease of chronic fuel excess that outweighs the adaptive mechanisms driving safe disposal of energy overload in genetically and epigenetically susceptible individuals [3,4].

Among all pathophysiological mechanisms of T2D, insulin resistance is one of the most long-lasting concepts. It still is a key element nowadays. Euglycemic insulin clamp studies established that insulin resistance precedes the onset of diabetes mellitus. Insulin resistance sites are both the liver and the muscle.

Today it is classical knowledge that the rate of hepatic gluconeogenesis is increased, leading to a high glucose output, even though insulin concentrations in the blood are twice to three times above the normal. This finding led the scientists to postulate the phenomenon of hepatic resistance to the suppression effect of insulin on glucose production [5]. Then again, other research teams proved that causes leading to a high liver glucose output are multiple, including high concentrations of plasma glucagon and a high hepatic sensitivity to glucagon actions [6], increased expression and activity of glucose-6-phosphatase (the rate-limiting enzyme for the liver glucose output) [7,8] and increased expression and activity of the gluconeogenesis rate-limiting enzymes: phosphoenolpyruvate carboxykinase and pyruvate carboxylase [9]. Insulin resistance of the skeletal muscle was also subject to extended research, only to find it has multiple explanations: low glucose intake in the muscle cells, decreased phosphorylation, glycogen synthesis, glycolysis and glucose oxidation [10-12]. The skeletal muscle also seems to be affected in T2D, exhibiting a low number of dysfunctional mitochondria [13]. The whole way, pathophysiological ramifications hidden under the general concept of insulin resistance seem to be complex and maybe not yet entirely known.

Even though hepatic and muscular insulin resistance certainly play a major role in T2D pathophysiology, overt hyperglycemia and diabetes only appear if β-cell dysfunction coexists [14]. Today the multiphasic evolution of the β-cell secretion is generally acknowledged, but retrospectively speaking, it must have been a complex process to be inferred. Insulin secretion is initially increased in the incipient stages of the disease, as the pancreas tries to cope with the glycemic rise induced by the liver and muscle insulin resistance. In time, the β cells become unable to maintain this increased insulin secretion anymore, and thus the insulin output starts to decrease, leaving way to prediabetes and afterwards to overt T2D. Besides, both the increased hepatic glucose production and the low muscle glucose intake contribute to aggravate hyperglycemia; the phenomenon of glucotoxicity adds to the previous ones, becoming a supplemental stress factor for the β-cell, further decreasing its insulin secretion. A true vicious circle is closed. Last but not least, a progressive decrease in the β-cell mass accompanies the reduced β-cell function. Even though susceptibility mechanisms leading to β-cell failure act heterogeneously at the beginning of the process, glucotoxic and lipotoxic mechanisms seem to predominate in most patients once considerable hyperglycemia has developed, thus leading to an accelerated β-cell deficiency and loss [4]. Some of the newer drugs introduced in the treatment of T2D are hoped to preserve the β cells insulin secretion and prevent or at least delay β-cell apoptosis [15].

The time T2D pathophysiology was dominated by the triumvirate concept, pancreas malfunction seemed limited to β-cell dysfunction. The scientific concept has changed, and other cells, tissues or organs were added to the classical triumvirate. It is generally accepted today that T2D patients exhibit both an increased glucagon secretion from the pancreatic α-cell, as well as a higher liver sensitivity to glucagon

actions [6]. Even though hyperglycemic hyperinsulinemic type 2 diabetics should supress their glucagon secretion in the α-cells in response to feedback loops, they display in fact increased glucagon blood concentrations, thus contributing to the high hepatic glucose output.

An old notion only to be rediscovered in the last decades pertains to the incretin effect. The intestine-secreted factors that increase insulin secretion in response to meals were identified during the 60's. It took a few years before the acknowledgement of a reduced incretin effect in T2D. The two incretin hormones, Glucagon Like Peptide 1 (GLP-1) and Glucose dependent Insulinotropic Polypeptide (GIP), exert an important role in glucose homeostasis: both of them stimulate β-cell insulin secretion, while GLP-1 has other effects unshared by GIP: inhibition of glucagon secretion, delayed gastric emptying and decreased appetite. Researchers speak about the phenomenon of resistance to GLP-1 and/or GIP, considering it another form of glucotoxicity [16]. Nevertheless, although an abnormal incretin effect and its consequences upon glucagon secretion definitely contributes to the aggravation of pre-existing hyperglycemia, it is less probable for it to be a primary mechanism in the pathogenesis of T2D [17].

Progress of medical knowledge in the recent years also added the abnormal adipocyte metabolism to the pathophysiological mechanisms of T2D. Thereby, adipose cells are resistant to the antilipolytic effects of insulin, leading to an increased concentration of free fatty acids [18]. As direct consequences, these circulating free fatty acids stimulate the hepatic gluconeogenesis, increase the liver and muscle resistance to insulin and negatively impact insulin secretion in the β cells, a phenomenon known as lipotoxicity [19,20]. In normal conditions, healthy cells in the white adipose tissue have a good ability to store fat, mostly in the subcutaneous adipose tissue, therefore preventing lipids to spill over towards other organs. On the contrary, the insulin-resistant, hypertrophic adipocytes have a low capacity to store lipids. Fat deposits tend to predominate at the level of visceral adipose tissue, which is less "metabolically healthy". When the adipocyte storage capacity is exceeded, lipids overflow in the muscle, liver and β cells, leading to muscular and hepatic insulin resistance and to β-cell dysfunction (another form of lipotoxicity). In addition, lipids that cannot be stored within adipocytes reach the smooth muscle cells in the arterial wall, thus accelerating atherosclerosis [16]. Numerous studies of the last years indicated a chronic inflammatory status in the adipocytes, which secrete excessive amounts of cytokines (TNF-α, IL-6, resistin), thus inducing insulin resistance, inflammation and rapid atherosclerosis progression; low adipocyte secretion of insulin-sensitizing adipocytokines such as adiponectin is also well-known [3,18].

As knowledge about T2D pathophysiology extended progressively, the kidney was also identified as having an important role in glucose homeostasis. Healthy people, with a glomerular filtration rate of 180 l/day and glycemic levels of approximately 100 mg/dl, filter through the kidneys approximately 180 g glucose/day. 90% of this amount of glucose is reabsorbed in the proximal convoluted tubule by the sodium-glucose co-transporters 2 (SGLT-2), and the rest of 10% is reabsorbed by the sodium-glucose co-transporters 1 (SGLT-1). In normal conditions, all filtered glucose is reabsorbed by these two co-transporters, hence no glucose molecules are eliminated in the final urine as long as glycemic values do not exceed 180-200 mg/dl. Only in the recent years it was found out that T2D features higher values for both the renal threshold of glucose urinary output and the maximal tubular capacity of glucose reabsorption. Thereby the

diabetic kidney reabsorbs more glucose, thus aggravating hyperglycemia [21,22].

Last but not least, the range of tissues and organs involved in the pathophysiology of T2D broadened enough as to include today the central nervous system. In healthy people insulin is sending to the brain signals that stop food ingestion and therefore reduce energy intake. In obese or T2D patients the appetite centres become resistant to insulin actions, so these individuals keep the same appetite, even though having a hyperinsulinemic state [23]. Other neurotransmitter dysfunctions were identified during the last years, such as an increased resistance to leptin's effect to suppress appetite, low dopamine levels in the hypothalamus and high levels of catecholamines in the central nervous system [24-27].

As mentioned before, all these pathophysiological defects appear, in different proportions, on the ground of genetic and epigenetic predisposition to T2D. Knowledge on this matter broadened considerably in the last years, only to highlight the complex nature of this susceptibility. First, genetic heritability seems to have a diverse nature in T2D, as the number of confirmed susceptibility loci is already higher than 60 and continuously rising. Second, these predisposing genes interact heterogeneously with environmental factors during gestation, early childhood and later in life [3]. Intrauterine growth restriction seems to correlate with the most important of all adult chronic diseases, including T2D, most probably by a mismatch between the epigenetic regulation for low fuel intake and the later high-energy intake so common in the modern lifestyle featuring high-calorie diets and sedentary habit [3,28]. Early life programming may affect the neurohormonal network driving weight control and the proper development of pancreatic islets [29]. Vitamin B_{12} deficiency during gestation, particularly in mothers replete for folic acid, postnatal vitamin D deficiency or excess iron storage, abnormal gut microbiota also seem to be involved in the pathophysiological pathways leading to T2D [30-33].

Theoretical knowledge increases its value if clinical applications can be identified. Translating theory into practice, new medications intercepting the newly described mechanisms subsequently appeared in the clinical research and then on the market. Older medications sometimes regressed in the hierarchy of medical prescriptions, or new valences were discovered for them, such as it is the case of metformin. Early diagnosis of diabetes and early initiation of drug therapy can sometimes offer a better chance of evolution, as the progressive β-cell dysfunction may be avoided or at least delayed. On the other hand, many patients need in time combinations of different drugs, which is only to remind us about the complexity of T2D pathogenesis and also of the progressive nature of the disease. Moreover, as other pathological conditions frequently associate to T2D, another therapeutic concept has emerged, namely the need for an antidiabetic drug to exert beneficial effects on these associated comorbidities. It is all these aspects that suggest the terminus point of the long journey towards the complete appraisal of the T2D pathophysiology, and thereby towards the utmost extension of specific medication range, is still far away or maybe unreachable.

REFERENCES

1. DeFronzo RA. Lilly Lecture: the triumvirate: beta cell, muscle, liver: a collusion responsible for NIDDM. *Diabetes* 37: 667-687, 1988.

2. DeFronzo RA. Banting Lecture: from the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes* 58: 773-795, 2009.

3. Nolan CJ, Damm P, Prentki M. Type 2 diabetes across generations: from pathophysiology to prevention and management. *Lancet* 378: 169-181, 2011.

4. Prentki M, Nolan CJ. Islet β cell failure in type 2 diabetes. *J Clin Invest* 116: 1802-1812, 2006.

5. Girard J. The inhibitory effects of insulin on hepatic glucose production are both direct and indirect. *Diabetes* 55 [Suppl. 2]: S65-S69, 2006.

6. Matsuda M, DeFronzo RA, Glass L et al. Glucagon dose-response curve for hepatic glucose production and glucose disposal in type 2 diabetic patients and normal individuals. *Metabolism* 51: 1111-1119, 2002.

7. Clore JN, Stillman J, Sugerman H. Glucose-6-phosphatase flux in vitro is increased in type 2 diabetes. *Diabetes* 49: 969-974, 2000.

8. Haeusler RA, Camastra S, Astiarraga B, Nannipieri M, Anselmino M, Ferrannini E. Decreased expression of hepatic glucokinase in type 2 diabetes. *Mol Metab* 18; 4: 222-226, 2014.

9. Gastaldelli A, Baldi S, Pettiti M et al. Influence of obesity and type 2 diabetes on gluconeogenesis and glucose output in humans: a quantitative study. *Diabetes* 49: 1367-1373, 2000.

10. Pendergrass M, Bertoldo A, Bonadonna R et al. Muscle glucose transport and phosphorylation in type 2 diabetic, obese nondiabetic, and genetically predisposed individuals. *Am J Physiol Endocrinol Metab* 292: E92-100, 2007.

11. DeFronzo RA. Insulin resistance, lipotoxicity, type 2 diabetes and atherosclerosis: the missing links. The Claude Bernard Lecture 2009. *Diabetologia* 53: 1270-1287, 2010.

12. Bajaj M, Defronzo RA. Metabolic and molecular basis of insulin resistance. *J Nucl Cardiol* 10: 311-323, 2003.

13. Patti ME, Corvera S. The role of mitochondria in the pathogenesis of type 2 diabetes. *Endocr Rev* 31: 364-395, 2010.

14. Abdul-Ghani M, Tripathy D, DeFronzo RA. Contribution of beta cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. *Diabetes Care* 29: 1130–1139, 2006.

15. Huang CJ, Lin CY, Haataja L et al. High expression rates of human islet amyloid polypeptide induce endoplasmic reticulum stress mediated beta-cell apoptosis, a characteristic of humans with type 2 but not type 1 diabetes. *Diabetes* 56: 2016-2027, 2007.

16. DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. In: *International Textbook of Diabetes Mellitus, 4th edition.* DeFronzo RA, Ferrannini E, Zimmet P, Alberti KGMM (eds). Wiley Blackwell, Chichester, pp 371-400, 2015.

17. Meier JJ, Nauck MA. Is the diminished incretin effect in type 2 diabetes just an epi-phenomenon of impaired β-cell function? *Diabetes* 59: 1117-1125, 2010.

18. Bays HE, González-Campoy JM, Bray GA et al. Pathogenic potential of adipose tissue and metabolic consequences of adipocyte hypertrophy and increased visceral adiposity. *Expert Rev Cardiovasc Ther* 6: 343-368, 2008.

19. Kashyap SR, Belfort R, Berria R et al. Discordant effects of a chronic physiological increase in plasma FFA on insulin signaling in healthy subjects with or without a family history of type 2 diabetes. *Am J Physiol Endocrinol Metab* 287: E537-546, 2004.

20. Belfort R, Mandarino L, Kashyap S et al. Dose-response effect of elevated plasma free fatty acid on insulin signaling. *Diabetes* 54: 1640-1648, 2005.

21. Abdul-Ghani MA, Norton L, DeFronzo RA. Role of sodium-glucose cotransporter 2 (SGLT 2) inhibitors in the treatment of type 2 diabetes. *Endocr Rev* 32: 515-531, 2011.

22. DeFronzo RA, Hompesch M, Kasichayanula S et al. Characterization of renal glucose reabsorption in response to dapagliflozin in healthy subjects and subjects with type 2 diabetes. *Diabetes Care* 36: 3169-3176, 2013.

23. Plum L, Belgardt BF, Brüning JC. Central insulin action in energy and glucose homeostasis. *J Clin Invest* 116: 1761-1766, 2006.

24. Kleinridders A, Cai W, Cappellucci L et al. Insulin resistance in brain alters dopamine turnover and causes behavioral disorders. *Proc Natl Acad Sci USA* 112: 3463-3468, 2015.

25. DeFronzo RA. Bromocriptine: a sympatholytic, D2-dopamine agonist for the treatment of type 2 diabetes. *Diabetes Care* 34: 789-794, 2011.

26. Derghal A, Djelloul M, Airault C et al. Leptin is required for hypothalamic regulation of miRNAs targeting POMC 3'UTR. *Front Cell Neurosci* 9: 172, 2015.

27. DeFronzo RA, **Triplitt CL**, **Abdul-Ghani M**, **Cersosimo E**. Novel agents for the treatment of type 2 diabetes. *Diabetes Spectr* 27: 100-112, 2014.

28. Pinney SE, Simmons RA. Epigenetic mechanisms in the development of type 2 diabetes. *Trends Endocrinol Metab* 21: 223-229, 2010.

29. Chen H, Simar D, Morris MJ. Hypothalamic neuroendocrine circuitry is programmed by maternal obesity: interaction with postnatal nutritional environment. *PloS One* 4: e6259, 2009.

30. Yajnik CS, Deshpande SS, Jackson AA et al. Vitamin B12 and folate concentrations during pregnancy and insulin resistance in the off spring: the Pune Maternal Nutrition Study. *Diabetologia* 51: 29-38, 2008.

31. Rajpathak SN, Crandall JP, Wylie-Rosett J, Kabat GC, Rohan TE, Hu FB. The role of iron in type 2 diabetes in humans. *Biochim Biophys Acta* 1790: 671-681, 2009.

32. Barrett H, McElduff A. Vitamin D and pregnancy: an old problem revisited. *Best Pract Res Clin Endocrinol Metab* 24: 527-539, 2010.

33. Musso G, Gambino R, Cassader M. Obesity, diabetes, and gut microbiota: the hygiene hypothesis expanded? *Diabetes Care* 33: 2277-2284, 2010.