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The primary aim of *World Journal of Diabetes* (WJD, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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Free fatty acids, glucose, and insulin in type 2 diabetes mellitus

Rob NM Weijers

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Abstract

Xu *et al* used the HOMA2 model to estimate the β -cell function and insulin resistance levels in an individual from simultaneously measured fasting plasma glucose and fasting plasma insulin levels. This method is based on the assumption that the glucose-insulin axis is central for the metabolic activities, which led to type 2 diabetes. However, significant downregulation of both the *NKX2-1* gene and the *TPD52L3* gene force an increase in the release of free fatty acids (FFAs) into the blood circulation, which leads to a marked reduction in membrane flexibility. These data favor a FFA-glucose-insulin axis. The authors are invited to extend their study with the introduction of the saturation index (number of carbon-carbon double bonds per 100 fatty-acyl chains), as observed in erythrocytes.

Key Words: Free fatty acids; Membrane flexibility; *NKX2-1* gene; RNA sequencing; Type 2 diabetes; *TPD52L-3* gene; Unsaturation index

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Core Tip: A substantial reduction in both *NKX2-1* and *TPD52L3* proteins is largely responsible for a reduction in carbon-carbon double bonds of phospholipids which, in turn, translates into the redistribution of the lateral pressure profile, and thereby reduces the transport speed of glucose molecules across the cell membrane. Consequently, the amount of plasma glucose entering the β -cell *via* GLUT2 gives a false negative result. Also the redistribution of the lateral pressure profile lowers the insulin release from β -cells into the blood circulation. Both phenomena cause the onset of type 2 diabetes mellitus.

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TO THE EDITOR

In the August 2021 issue of *World J Diabetes*, Xu *et al*[1] reported on the association of β -cell function and insulin resistance with pediatric type 2 diabetes among Chinese children. The term "insulin resistance" in the article needs additional clarification and review.

As early as 1933, there was as yet no general agreement as to the definition of the term "insulin resistance" and thus gaps in research and clinical care persisted. The breakthrough of the correct description of the term was a clear example of serendipity. A study by Takematsu *et al*[2] compared genome-wide changes in the gene expression in skin between patients with type 2 diabetes and non-diabetic patients *via* RNA sequencing, resulting in the identification of 64 significantly upregulated genes and 120 significantly downregulated genes. Among these regulated genes, the most downregulated gene was *NKX2-1*, with a down regulation value of 3.7×10^{-9} , and in the metabolism category the most downregulated gene was *TPD52L3*, also with a down regulation value of 3.7×10^{-9} . The latter gene has not been linked to type 2 diabetes.

Defective *NKX2-1* production is associated with an essential reduction in the activity of the mitochondrial respiratory chain complex, which reduces ATP production. This idea is supported by the data from a study suggesting that a dysregulation of intramyocellular fatty acid metabolism in the offspring of patients with type 2 diabetes was associated with an inherited defect in mitochondrial oxidative phosphorylation[3]. To restore ATP production, the β -oxidation of fatty acids provides assistance by increasing the levels of plasma free fatty acids (FFAs) *via* hydrolysis. Calculation of the saturation indices (number of cis carbon-carbon double bonds per 100 fatty acyl-chains[4]) of FFAs released from human white fat cells and human plasma FFAs in healthy controls reveals that the index of the former is substantially lower (85.5 and 191.9, respectively; $\Delta = 55.4\%$)[5]. Thus, we can conclude that an increase in the release of FFAs into the blood circulation due to an essential reduction in the activity of the mitochondrial respiratory chain complex leads to a marked reduction in the unsaturated index.

In a previous study, the author found that, in brown adipose tissue, the mitochondrial population exists as two subclasses: cytoplasmic mitochondria that do not adhere to lipid droplets and mitochondria that do adhere to lipid droplets. The lipid droplets are cytosolic storage organelles consisting mostly of neutral lipids and enclosed by a phospholipid monolayer membrane[6]. This monolayer has persistent surface packing defects, whereby neutral lipids are accessible to the aqueous cytoplasm and the blood circulation. The idea is that *TPD52L3* covers these defects in healthy individuals. Thus, it seems likely that the significant downregulation of *TPD52L3* causes an increase in FFAs in the blood circulation and also lowers the saturation index.

Thus, we can conclude that the downregulation of *NKX2-1* and *TPD52L3* forces an increase in the release of FFAs into the blood circulation due to the leaky lipid droplets and the essential reduction in mitochondrial oxidative and phosphorylation activity, and thereby reduces the unsaturation index, as demonstrated in impaired glucose tolerance[7] (Table 5 in Weijers[7]), gestational diabetes mellitus[7] (Table 5 in Weijers[7]), and type 2 diabetes[4] (Table 2 in Weijers[4]). These phenomena lead to a marked shift from unsaturated to saturated acyl chains in the membrane phospholipids, which redistributes the lateral pressure profile of the cell membrane[8]. The redistribution of this profile narrows the pore diameter of the transmembrane glucose transport channels of all class I glucose transporter proteins, and thus reduces the rate of transport of glucose molecules across the cell membrane, initiating the onset of type 2 diabetes[7].

The following conclusions can be drawn from the presented information. First, type 2 diabetes is characterized by reduced membrane flexibility in the pancreatic β -cell, which adversely affects the amount of glucose entering the β -cell *via* GLUT2, and thereby lowers the synthesis of the necessary amount of circulating insulin molecules. Secondly, fusion of the insulin-containing granule with the β -cell plasma membrane, followed by the formation of a suitable pore diameter for insulin transport into the blood circulation, requires high flexibility in both the granule-cell membrane and the β -cell membrane. The reduction in the flexibility of both membranes lowers the insulin release from the β -cell into the blood circulation. These facts underline the fact that a reduction in membrane flexibility lowers not only the rate of transport of glucose molecules into the β -cell but also the rate of transport of insulin molecules from the β -cell into the blood circulation.

Up to now, it has been thought that the glucose-insulin axis is central to the metabolic activities that lead to type 2 diabetes. A publication in 1992 is an exception in this respect, having the title: "What if Minkowski had been ageusic? An alternative angle on diabetes"[9]. This study suggested that the basic pathophysiological mechanisms of type 2 diabetes might be more readily understood if viewed in the context of underlying abnormalities of lipid metabolism. Xu *et al*[1] used the HOMA2 model to estimate β -cell function and insulin resistance levels in a pediatric individual from simultaneously measured fasting serum glucose and fasting serum insulin concentrations. The summarized phenomena, in my opinion, are a scientific basis for the idea that membrane flexibility plays an important part in the onset of type 2 diabetes.

Therefore, I suggest that Xu *et al*[1] add to their article a follow-up study including the unsaturation index, as a parameter for membrane flexibility, based on the erythrocyte membrane fatty-acid compositions because, at the most basic level, the basal metabolic rate of a cell is directly linked to its cell

membrane's acyl composition[10]. A strong argument in favor of the FFA-glucose-insulin axis is the observation that in persons at high risk for type 2 diabetes, the incidence of diabetes was reduced by 58% with lifestyle intervention and by 31% with metformin, as compared with placebo[11]. It seems likely that physical activity, after all, raises the levels of the unsaturation index, in contrast to metformin.

FOOTNOTES

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REFERENCES

- 1 **Xu ZR**, Du HW, Cui LW, Zheng RX, Li GM, Wei HY, Lu FY, Chen LL, Wu CS, Zhang SX, Zhang SL, Liu F, Zhang MY, Pei Z, Sun CJ, Wu J, Luo FH. Association of β -cell function and insulin resistance with pediatric type 2 diabetes among Chinese children. *World J Diabetes* 2021; **12**: 1292-1303 [PMID: 34512894 DOI: 10.4239/wjd.v12.i8.1292]
- 2 **Takematsu E**, Spencer A, Auster J, Chen PC, Graham A, Martin P, Baker AB. Genome wide analysis of gene expression changes in skin from patients with type 2 diabetes. *PLoS One* 2020; **15**: e0225267 [PMID: 32084158 DOI: 10.1371/journal.pone.0225267]
- 3 **Petersen KF**, Dufour S, Befroy D, Garcia R, Shulman GI. Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. *N Engl J Med* 2004; **350**: 664-671 [PMID: 14960743 DOI: 10.1056/NEJMoa031314]
- 4 **Weijers RNM**. Unsaturation index and type 2 diabetes: unknown, unloved. *World J Meta-Anal* 2015; **3**: 89-92 [DOI: 10.13105/wjma.v3.i2.89]
- 5 **Weijers RN**. Membrane flexibility, free fatty acids, and the onset of vascular and neurological lesions in type 2 diabetes. *J Diabetes Metab Disord* 2015; **15**: 13 [PMID: 27123439 DOI: 10.1186/s40200-016-0235-9]
- 6 **Weijers RNM**. Identification of downregulation of TPD52-Like3 gene and NKX2-1 gene in type 2 diabetes mellitus via RNA sequencing. *Arch Diab Obes* 2020; **3**: 277-281 [DOI: 10.32474/ado.2020.03.000156]
- 7 **Weijers RN**. Fundamentals about onset and progressive disease character of type 2 diabetes mellitus. *World J Diabetes* 2020; **11**: 165-181 [PMID: 32477453 DOI: 10.4239/wjd.v11.i5.165]
- 8 **Cantor RS**. Lateral pressures in cell membranes: a mechanism for modulation of protein function. *J Phys Chem B* 1997; **101**: 1723-1725 [DOI: 10.1021/jp963911x]
- 9 **McGarry JD**. What if Minkowski had been ageusic? *Science* 1992; **258**: 766-770 [PMID: 1439783 DOI: 10.1126/science.1439783]
- 10 **Hulbert AJ**. Life, death and membrane bilayers. *J Exp Biol* 2003; **206**: 2303-2311 [PMID: 12796449 DOI: 10.1242/jeb.00399]
- 11 **Knowler WC**, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; **346**: 393-403 [PMID: 11832527 DOI: 10.1056/NEJMoa012512]



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