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Mini Review

The Relationship Between the Type 2 Diabetes Mellitus: Insulin Resistance Loses Relevance

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Abstract

The interplay between insulin sensitivity and insulin resistance plays a key role in the development and persistence of type 2 diabetes mellitus. While there are still questions about an universally accepted definition for insulin resistance, it is commonly described as a condition in which cells do not respond adequately to insulin. However, new insights indicate that a more scientific interplay exists between insulin sensitivity and membrane flexibility, which plays a key role in the development and persistence of the type 2 diabetic state. Results from this study highlights the significance of membrane flexibility and raise concerns about the dangers associated with the term 'insulin resistance'. Aerobic exercise training based on the level of the unsaturation index, a measure of unsaturation that is defined as the mean number of cis double bonds per 100 fatty acid, represents a great step forward in the development of precision medicine in view of type 2 diabetes mellitus.

ABBREVIATIONS

TPD52L3: Tumor protein D52-like3; NKX2-1: NK2 Homeobox 1; ATP: Adenosine Triphosphate; GLUT: Glucose Transporter

INTRODUCTION

The term 'insulin resistance' was introduced by Falta *et al*. in the medical literature nearly ninety years ago [1]. While there is no universally accepted definition for 'insulin resistance', it is commonly described as a condition in which cells do not respond adequately to insulin, leading to impaired glucose intake and increased blood sugar levels. Insulin resistance is often associated with type 2 diabetes mellitus. Examining the risks associated with 'insulin resistance', this study emphasises the value of membrane flexibility in type 2 diabetes.

To investigate alterations in gene expression in the skin of individuals diagnosed with type 2 diabetes in comparison to those without, a recent study used next-generation RNA sequencing. The research found two genes, *TPD52L3* (tumor protein D52-like3) and *NKX2-1*, which are involved in both gene regulation and gene metabolism. Both genes showed a significant downregulation value of 3.7×10^{-9} in patients with type 2 diabetes compared to those without the disease [2].

Wound healing and type 2 diabetes do not correlate with the *TPD52L3* gene. However, a study using exogenous TPD52 protein expression in cultured cells observed increased lipid bodies [3]. Adipocytes employ lipid bodies as specialised organelles to store excess fatty acids. Researchers discovered that the *TPD52* and *TPD52L3* genes were 67.9% homologous, with 63 positions in their sequences being the same and 42 positions being similar [4]. This suggests that TPD52L3 likely plays a role in lipid storage in fat cells, potentially impacting free fatty acids release into the blood stream.

In addition to cytoplasmic mitochondria there are also peri-droplet mitochondria [5]. The latter mitochondria bound to lipid droplets, which are cytosolic storage organelles consisting of neutral lipids and enclosed by phospholipid *mono*layer membranes. The idea is that membrane leakage defects are covered by TPD52L3 proteins in healthy individuals. Most likely, a significant down regulation of TPD52L3 causes an increase in free fatty acids in the blood circulation.

A transcription factor called NKX2-1 showed less activity in the mitochondrial respiratory chain complex. This changed many cellular processes, such as the production of ATP [6]. In addition to increasing circulating free fatty acids, the β-oxidation of fatty acids is crucial for replenishing ATP production, as it increases plasma-free fatty acids through hydrolysis, thereby enhancing energy generation. A crucial feature of type 2 diabetes mellitus is diminished mitochondrial activity [7].

The unsaturation index, defined as the number of *cis* carbon-carbon double bonds per 100 fatty acyl-chains, exhibits a statistically significant difference of 191.9 and 85.5 between the serum-free fatty acids of healthy controls and those generated

from human white fat cells [8]. The release of these unsaturated free fatty acids significantly reduces the unsaturation index of vascular and erythrocyte membranes, resulting in decreased membrane flexibility.

Glycerophospholipids are the main membrane phospholipids naturally found in eukaryotes. The hydrocarbon region of the molecule, formed by the two fatty acyl chains, is roughly cylindrical and can easily align in parallel to create extended membrane sheets. The area (A) of a lipid molecule is determined by the surface area (A) of its cylindrical segment. Experimental values of A were obtained for various fully hydrated fluid-phase artificial phosphatidylcholine lipid bilayer samples using electron density profiles. Notably, these profiles consistently showed that unsaturation of the fatty acyl chains yields a higher value of A compared to saturation [9]. Membrane flexibility decreases when the distance between fatty acyl chains shortens, reducing the number of *cis*-carbon-carbon double bonds. This results in increased interaction energy between chains, decreasing membrane flexibility.

Proteins within cell membranes may be impacted by lipid composition changes. Even slight variations in lateral pressure across a bilayer membrane can significantly alter the conformational distribution of encapsulated proteins [10]. Compared to healthy individuals, type 2 diabetes mellitus is characterized by a shortage in *cis*-carbon-carbon double bonds, which can initiate the redistribution process in membrane phospholipids. Membrane flexibility decreases when the area (A) of lipid molecules in the cell membrane is reduced. This reduced flexibility may hinder the conformational changes and movement of proteins within the membrane, such as glucose transporters. The data are becoming clear that the poly-unsaturation of membrane phospholipids is an important feature for the biophysical properties of membranes and membrane proteins. In particular, it regulates the function of transmembrane glucose transport [11].

Once insulin monomers are synthesised in the β-cell, they aggregate to form stable hexamers comprising six monomer insulin molecules, with a molecular weight of 36,000. These hexamers, contained within mature intracellular vesicles, are transported to the plasma membrane of the β-cell. The fusion of the vesicle membrane with the β-cell plasma membrane creates a fusion pore, enabling the release of monomer insulin molecules into the blood stream. Notably, the monomer insulin molecule, measuring 30 Å in width and 35 Å in height, is significantly larger than glucose molecules which are approximately 10 Å in size. Consequently, substantial flexibility is required in both the vesicle membrane and the β-cell plasma membrane to facilitate transport. In individuals with type 2 diabetes, the reduced unsaturation index leads to impaired membrane flexibility, resulting in a slower and diminished rate of transmembrane insulin transport into the blood stream.

The aforementioned findings offer a plausible solution for insulin resistance's role in the pathogenesis of type 2 diabetes. The decrease in cis-carbon-carbon double bonds in phospholipid membranes is primarily attributed to the significant downregulation of NKX2-1 and TPD52L3. This decrease leads to a reduction in the cross-sectional area (A) of the cylindrical portion of phospholipid molecules, resulting in increased attractive forces between acyl chains. Consequently, the lateral pressure within cellular membranes is redistributed, causing a decrease in the size of all Class 1 GLUT proteins. This, in turn, reduces the rate of glucose transport across the cell membrane. The experimental results align with biophysical and structural research, highlighting the crucial role of lipid-protein interactions in influencing protein folding and stability [12-15]. The clinical implications of the Diabetes Prevention Program Research Group's findings are very promising. The results indicate that lifestyle intervention decreased the risk of type 2 diabetes in high-risk individuals by 50%, while metformin resulted in a 31% decrease compared to placebo [16]. This insightful observation on treating type 2 diabetes deserves more recognition and focus.

An important outcome and a crucial feature in the etiology of type 2 diabetes mellitus is a marked reduction in the insulin sensitivity compared with the glucose effectiveness (56.6 %, and 24.1 %, respectively) [Table 1]. Regarding the insulin sensitivity, this result shows unequivocally that the production of insulin needs twice a passage of the β-cell's plasma membrane, once the transmembrane glucose transport, and thereafter the transmembrane insulin transport in the blood stream. However, the insulin-independent glucose removal rate uses only once a glucose passage of the β-cell's plasma membrane.

Multiple research studies have consistently demonstrated that lifestyle change treatment can effectively counteract the decline in membrane flexibility by increasing the membrane unsaturation index. Therefore, incorporating the unsaturation index into therapy regimens is highly recommended. By adopting this approach, we can better meet the needs of individuals with type 2 diabetes and strive to restore their membrane flexibility to normal levels. Furthermore, it is essential to reexamine the concept of 'insulin resistance'. The initial hypothesis that cells do not respond to insulin has been proven incorrect. Instead, the cell membrane plays a crucial role in regulating glucose transport rates. As a result, the concept of 'insulin resistance' becomes less significant, particularly when considering the vital function of membrane flexibility in glucose transport.

It is not unlikely that severe obesity and minimal controlled

Table 1: Quantification of glucose effectiveness and insulin sensitivity using two-compartment minimum models.

Units	Control subjects	Type 2 diabetes	P value	Δ(%)	Tracer
S_G					
h^{-1}	0.41 ± 0.04	0.33 ± 0.02	< 0.001	19.5	^{13}C
h^{-1}	0.52 ± 0.05	0.37 ± 0.02	< 0.001	28.8	^{2}H
Average				**24.1**	
S_I					
$pmol•L^{-1}•h^{-1}$	0.0082 ± 0.0012	0.0036 ± 0.0006	< 0.001	56.1	^{13}C
$pmol•L^{-1}•h^{-1}$	0.0098 ± 0.0013	0.0042 ± 0.0008	< 0.001	57.1	^{2}H
average				**56.6**	

Note: S_G: glucose effectiveness; S_I: insulin sensitivity.

lifestyle obtain so many saturated fatty acids in the blood circulation that the reduction of the unsaturation index leads to an impaired membrane flexibility, resulting in a slower rate of transmembrane glucose transport and the beginning of type 2 diabetes mellitus.

It cannot be stressed enough that walking, jogging, a cycling are an important part of the lifestyle change treatment for individuals with type 2 diabetes [17]. By increasing the membrane unsaturation index through aerobic exercise training, this treatment can adequately compensate for the loss of membrane flexibility as shown in numerous studies. Therefore, integrating the unsaturation index evaluation into the treatment protocol is advisable. This approach can help normalise membrane flexibility in individuals with type 2 diabetes and better meet their needs. Additionally, it is crucial to reexamine the concept of 'insulin resistance'. The initial idea that insulin has no impact on cells is incorrect. In reality, glucose transport rates are controlled by the cell membrane fatty acid composition. Thus, when considering the significant influence of the membrane flexibility on glucose transport the concept of 'insulin resistance' becomes outdated.

Author contributions

RNM: Conceptualization, Writing—original draft.

Conflicts of interest

This study was carried out without any commercial or financial relationships that could be perceived as a potential conflict of interest.

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