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Review Article

Oxidative Status in Etiology of Type 2 Diabetes

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Abstract

This review focuses on the relationship between oxidative status as measured by the systemic levels of lipid peroxidation markers F2-isoprostanesand etiology of type 2 diabetes. Elevated levels F2-isoprostaneswere found in obesity, insulin resistance, impaired glucose tolerance and type 2 diabetes. It was hypothesized that increased F2-isoprostanelevels reflect the obesity-induced oxidative stress that promotes the development of type 2 diabetes. The most convincing evidence against such an interpretation is the well-accepted role of physical activity in protecting against type 2 diabetes, given that physical activity increases F2-isoprostane levels. Adding to this evidence, the prospective studies show that individuals with higher levels of urinary F2-isoprostanes have a lower risk of weight gain and type 2 diabetes, thereby directly contradicting the etiological relevance of elevated oxidative status in diabetes etiology. This review examines a new interpretation of F2-isoprostane levels as reflecting intensity of oxidative metabolism, a major endogenous source of reactive oxygen species, and specifically, the intensity of fat oxidation.

Keywords: F2-isoprostanes; Obesity; Type 2 diabetes; Epidemiology; Oxidative metabolism

Abbreviations

BMI: Body Mass Index; ROS: Reactive Oxygen Species

Oxidative Status

All aerobic organisms are constantly exposed to Reactive Oxygen Species (ROS) generated either by endogenous processes, such as cellular respiration and antibacterial defense, or by external oxidative exposures, such as ionizing radiation, smoking, and toxins [1]. ROS are highly reactive molecules that oxidize DNA, lipids, and proteins [1]. To counteract their damaging effects, aerobic organisms have developed multiple antioxidant defense systems [1]. Theoretically, ROS production and antioxidant defense set constitutive levels of oxidative status within cells, tissues, and at the systemic level. Whether or not this assumption is correct at the tissue level remains to be determined. However, the systemic levels of oxidative status measured by biomarkers of lipid peroxidation, F2-isoprostanes [2,3], represents a constitutive individual characteristic [4,5]. F2-isoprostanes are the only biomarkers of oxidative status that have been validated against established oxidative stressors in animal [6] and clinical [7] models. Thus, this review will focus on the relationship between F2-isoprostanes and type 2 diabetes as well as diabetes risk factors. Importantly, similar to other individual characteristics, such as BMI and blood pressure, the levels of urinary F2-isoprostanes can change within an individual during the lifetime. Such modifiable factors are important for epidemiological research, because – as opposed to unmodifiable factors (age, gender, and genetics) – they can be targeted by prevention strategies. This consideration is especially important for etiology of type 2 diabetes, a disease that proved to be preventable [8]. If elevated oxidative status promotes the development of type 2 diabetes, the disease could be prevented by reducing oxidative status via lifestyle modifications and/or pharmacological interventions. This consideration stimulated research of the relationships between oxidative status and type 2 diabetes as well as its risk factors.

Oxidative status and type 2 diabetes

The cross-sectional studies show direct association between systemic F2-isoprostane levels and type 2 diabetes [9-16]. Also, the early stage of diabetes, impaired glucose tolerance [12,17,18], the hallmark of diabetes etiology insulin resistance [19], and its main risk factor obesity [12,20,21] – all are associated with elevated systemic levels of F2-isoprostanes cross-sectionally. Naturally, these cross-sectional associations can be interpreted as evidence that elevated F2-isoprostane levels promote the development of type 2 diabetes.

However, three lines of evidence strongly contradict sucha hypothesis. The first is related to the assumption that antioxidant supplementation can shift pro-/antioxidant balance and thereby, prevent type 2 diabetes. This assumption and the aforementioned cross-sectional findings encouraged several randomized trials of type 2 diabetes prevention. Contrary to expectations, all large randomized trials of antioxidant supplementation failed to prevent type 2 diabetes [22-28]. In fact, a systematic review of the overall mortality in antioxidant trials concluded that "Beta-carotene and vitamin E seem to increase mortality, and so may higher doses of vitamin A" [29].Failure to prevent diabetes by antioxidant supplementation questions the hypothesis that elevated oxidative status promotes the development of type 2 diabetes.

The second line of evidence is related to physical exercise as one of the best preventive strategies in type 2 diabetes prevention [30,31]. Physical exercise undeniably increases F2-isoprostane levels for at least several hours [32]; whereas an increase in the basal levels of these biomarkers has been demonstrated only in some populations [33]. Over the years a sustained exercise training exposes an individual to repetitive sharp increases in oxidative status. Thus, there is a contradiction between the suggested harmful role of high oxidative status on one hand and the protective role of physical exercise that increases oxidative status on the other hand. Dr. James

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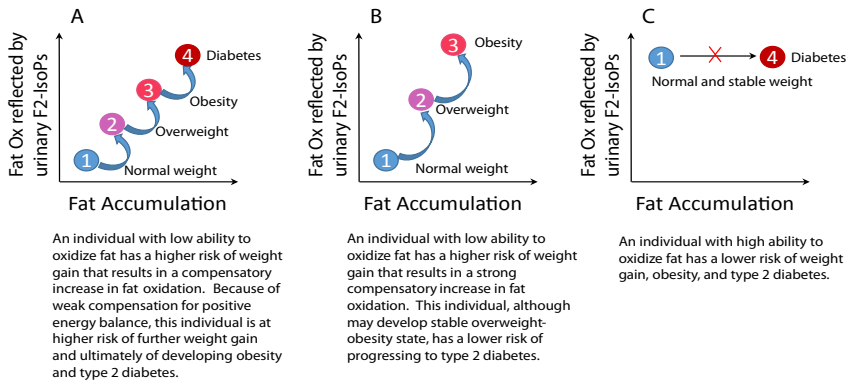

Figure 1: Proposed relationships between urinary F2-isoprostanes and fatty acid oxidation rates.

Watson published a biological hypothesis explaining why increased generation of ROS by physical exercise prevents the development of type 2 diabetes, namely by generating a "sufficient redox potential for disulfide bonds to be formed" [34].

The third and the ultimate line of evidence of a protective instead of causal role of elevated systemic F2-isoprostanes in etiology of type 2 diabetes come from the prospective studies. In two cohorts, elevated levels of F2-isoprostanes predicted lower risk of weight gain [21,35]. Moreover, high levels of F2-isoprostanes predicted lower risk of type 2 diabetes [36]. These prospective findings refute the hypothesis that elevated F2-isoprostane levels promote the development of type 2 diabetes. Hence, the prospective and cross-sectional data show opposite directions of the associations between F2-isoprostane levels and type 2 diabetes. How can this be explained?

The existing cross-sectional and prospective findings can be reconciled within the framework of a compensatory function. Within this framework, systemic levels of F2-isoprostanes can be interpreted as reflecting a compensatory mechanism that is related to etiology of obesity and type 2 diabetes.

Regulation of energy balance as a framework for understanding the connection between oxidative status and type 2 diabetes etiology

A compensatory mechanism involved in the maintenance of energy balance can explain the opposite direction of the cross-sectional and prospective associations between F2-isoprostane levels and obesity and type 2 diabetes risks.

Generally, a stable body weight constitutes balanced energy intake and energy expenditure. Positive energy balance occurs when energy intake exceeds energy expenditure and is manifested as an increase in body mass, with the majority of the gained mass being fat mass [37,38]. Correspondingly, negative energy balance occurs when energy expenditure exceeds energy intake and is manifested as a loss of body mass, with fat mass loss being the predominant component of this change as well. A physiological control of energy balance promotes shifts in energy expenditure to counteract both negative energy balance (by a decrease in energy expenditure) and positive energy balance (by an increase in energy expenditure). With fat mass being the predominant element of body mass changes, it is not surprising that fat oxidation plays an essential role in physiological control of energy balance [37-41]. Accordingly, in obese individuals the levels of fat oxidation rates on average are higher as a result of fat mass gain; and conversely, weight loss is associated with a decrease in fat oxidation rates. At the same time, efficient fat oxidation lowers the risk of weight gain and thereby, the risk of obesity and type 2 diabetes [37-41] (Figure 1). Thus, fat oxidation rates are positively associated with obesity and type 2 diabetes (fat oxidation rates increase in type 2 diabetes also as a result of diminished ability to use glucose as a fuel source), whereas intensive fat oxidation reduces the risk of both conditions.

Is there a connection between F2-isoprostanes and fat oxidation rates? Such connection would explain the increased levels of F2-isoprostanes among obese individuals and diabetics as well as lower risks of weight gain and type 2 diabetes among individuals with elevated levels of these biomarkers [42].

Systemic levels of F2-isopeostanes and fatty acid oxidation

As biomarkers of systemic ROS levels, F2-isoprostanes are likely to reflect intensity of mitochondrial metabolism, which represents the major endogenous source of ROS (1). A connection between oxidative metabolism and F2-isoprostane levels can explain the observed increase in F2-isoprostanes during physical exercise as a reflection of increased oxidative metabolism and fatty acid oxidation specifically. Fatty acid oxidation increases with moderate physical activity as fat is the predominant contributor to muscle fuel metabolism; vice-versa muscles are the major organ for free fatty acid disposal [43-46]. Correspondingly, glucose uptake by skeletal muscle in the basal state accounts for only a small percentage of total glucose disappearance and only a minor proportion of peripheral oxygen consumption [47]. This suggests that the intensity of fatty acid oxidation by skeletal muscle is likely to determine whether an individual has higher or lower systemic ROS (and F2-isoprostane) levels. The fact that mitochondrial fatty acid oxidation produces higher levels of ROS as compared to glycolytic substrates [48] strongly supports the connection between increased oxidative status and intensive fat oxidation.

These hypothesized relationships between systemic F2-isoporstanes levels and fatty acid metabolism are further reinforced by several circumstantial evidence. For example, fat oxidation and urinary F2-isoporstanes both decrease in response to weight loss

[37,38,48]. Similar parallel relationships are found in racial groups: African Americans have lower levels of fat oxidation [49], and also lower levels of urinary F2-isoprostanes [50]. Furthermore, the rates of obesity and type 2 diabetes are greater among African Americans and low levels of fat oxidation are proposed as a metabolic trait predisposing African Americans to these conditions [49]. Other supporting evidence is the correlation between fasting levels of non-esterified fatty acids, that are known to stimulate fatty acid oxidation in skeletal muscles [43-46], and urinary F2-isoprostanes [51]. However, to the best of the author's knowledge, no direct evidence have been published that urinary F2-isoprostanes relates to the intensity of fat oxidation. For example, the proposed hypothesis predicts inverse relationship between respiratory quotient (low respiratory quotient indicates higher proportion of fat oxidation in fuel metabolism) and urinary F2-isoprostanes.

Within this framework (Figure 1), the well-established cross-sectional direct association of F2-isoprostane levels with obesity can be seen to represent a long-term adaptation to higher adiposity through increased fat oxidation. At the same time, slow fat oxidation – reflected by low urinary F2-isoprostane levels – would lead to weight gain. In the case of weak long-term adaptation, the cycle of increasing adiposity should persist, leading to the obesity-driven development of type 2 diabetes. Of importance, F2-isoprostane levels among African Americans showed no association with adiposity (measured as BMI), whereas a direct cross-sectional association with BMI was clearly evident among Caucasians [50]. This disconnect between F2-isoprostane levels and BMI in African Americans may signify weak long-term adaptation to higher adiposity, which potentially could help to explain the greater type 2 diabetes rates among African Americans.

Conclusion

Commonly, a statistically significant elevation of oxidative status markers has been interpreted as harmful oxidative stress [52]. A prominent example is the conventional view that the elevated F2-isoprostane levels in obesity represent obesity-induced oxidative stress and a mechanistic link between obesity and the risks of type 2 diabetes [53] and cardiovascular disease [54]. The most convincing evidence against such an interpretation is the well-accepted role of physical activity in protecting against the development of both type 2 diabetes and cardiovascular disease [31,55], given that physical activity actually increases F2-isoprostane levels at least for several hours. Adding to this evidence, the prospective studies show that individuals with higher levels of urinary F2-isoprostanes have a lower risk of weight gain [21,35] and type 2 diabetes [36]. These findings directly contradict the hypothesis that high oxidative status has etiological relevance in the development of diabetes; in fact, they suggest just the opposite – that an increase in F2-isoprostane levels may be beneficial in preventing diabetes and obesity. Congruent to these observations, multiple antioxidant supplementation trials so far have failed to prevent cardiovascular disease or type 2 diabetes [22-29]. Thus, the accumulating body of evidence emphasizes the need for a new interpretation of systemic oxidative status markers. The focus on fat oxidation as a physiological determinant of F2-isoprostane levels connects and sheds light on several observations that are otherwise unexplainable [42]. This hypothesis however does not rule out a possibility that locally elevated reactive oxygen/nitrogen species at the tissue level may promote development of pathological changes; but it argues that local oxidative stress contributes insignificantly to the systemic levels of oxidative status. Then, the systemic levels of F2-isoprostanes can be viewed as a beneficial metabolic trait reflecting healthy mitochondrial metabolism and fatty acid oxidation rates, allowing an effective physiological control of energy balance and thereby preventing obesity and type 2 diabetes.

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