Review Article

Systemic F_2-Isoprostane Levels in Predisposition to Obesity and Type 2 Diabetes: Emphasis on Racial Differences

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ABSTRACT

This review focuses on racial differences in systemic levels of lipid peroxidation markers F_2-isoprostanes as metabolic characteristics predisposing to obesity and type 2 diabetes. Elevated levels F_2-isoprostanes were found in obesity, type 2 diabetes and their comorbidities. It was hypothesized that increased F_2-isoprostane levels reflect the obesity-induced oxidative stress that promotes the development of type 2 diabetes. However, African Americans have lower levels of systemic F_2-isoprostane levels despite their predisposition to obesity and type 2 diabetes. The review summarizes new findings from epidemiological studies and a novel interpretation of metabolic determinants of systemic F_2-isoprostane levels as a favorable phenotype. Multiple observations indicate that systemic F_2-isoprostane levels reflect intensity of oxidative metabolism, a major endogenous source of reactive oxygen species, and specifically, the intensity of fat utilization. Evidence from multiple human studies proposes that targeting fat metabolism can be a productive race-specific strategy to address the existing racial health disparities. Urinary F_2-isoprostanes may provide the basis for targeted interventions to prevent obesity and type 2 diabetes among populations of African descent.

Keywords: Racial disparities; Obesity; Type 2 diabetes; Public health; Lipid peroxidation markers; Obesity-induced oxidative stress

Introduction

F_2-isoprostanes are formed during non-enzymatic oxidation of polyunsaturated fatty acids by different types of free radicals, including reactive oxygen species [1]. In these spontaneous reactions, the oxygen molecule is added to different positions within the fatty acid molecule, producing various isomers [1]. As such, F_2-isoprostanes present stable "footprints" of unstable free radicals that can be measured in human tissues and bodily fluids. Importantly for population studies and specifically, for interventions, F_2-isoprostanes are detectable in human blood and urine in the generally healthy population as well as in patients with pathological conditions [2-4]. Urinary F2-isoprostane levels have been validated as sensitive biomarkers of oxidative status in animal and clinical models [2,5]. Conventionally, these biomarkers are perceived as indicators of harmful oxidative stress. However, the emerging evidence supports a different interpretation of systemic F_2-isoprostane levels – as markers of intensive metabolism. In this review, we summarize the novel findings from human studies and their relevance to race-specific metabolic predisposition to obesity and type 2 diabetes. Our key objectives are the following: (1) review different factors and specifically, the role of race-specific metabolic predisposition in the existing health disparities; (2) present evidence for a need of race-specific interventions to address this metabolic component as substantiated by the findings from weight loss and physical activity/exercise interventions; (3) present the central idea of this review that systemic F_2-isoprostanes levels can serve as race-specific biomarkers of metabolic health; (4) describe relationships between systemic F_2-isoprostane levels and metabolic determinants of racial predisposition to obesity and type 2 diabetes; (5) describe the potential of interventions addressing the metabolic predisposition among African Americans, where F_2-isoprostanes can serve as a target and means to monitor the effects of such interventions.

Racial disparities in obesity and type 2 diabetes as a public health problem

It is well-known that African Americans are at increased risk of obesity and type 2 diabetes as compared to European Americans and suffer disproportionate morbidity and mortality due to these health problems [6-9]. Addressing this public health problem requires the understanding of its roots. Accordingly, the "Diabetes Research Strategic Plan 2011" accepted by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) specifies "Ethnic and Racial Disparities" (Special Needs for Special Populations) as one of its research priorities. It has been hypothesized that socioeconomic and obesogenic environment drives this racial health disparity [10-14]. This hypothesis postulates that readily available foods together with environmental quest discouraging physical activity contribute to the obesity trends in socially disadvantaged minority populations, including African American communities [15]. Ecological studies do not uniformly presented evidence for this environmental hypothesis; although the connection of obesity with the socioeconomic, built environment and food availability seems very intuitive. Indeed, the prevalence of obesity has increased in the U.S. over relatively a short period of the last several decades, suggesting that obesity is a predominantly

environmental disease [10,16-18]. Yet, some individuals maintain normal body weight despite obesogenic environment and vice versa, which implies differential susceptibility to obesogenic factors [19-21]. At the same time, multiple converging lines of evidence support the significance of the metabolic predisposition to obesity and type 2 diabetes among African Americans [22-27]. Such metabolic predisposition is most clearly manifested by an increased risk of type 2 diabetes among African

Americans at any level of BMI [28-30]. The question unanswered is: What are the practical approaches to reducing racial disparities in obesity and type 2 diabetes? [7,31]

Racial differences in response to weight loss interventions and cardiometabolic responses to exercise: A need to address specific metabolic component

African Americans tend to lose less weight than European Americans with similar treatments. Fitzgibbon et al. conducted a review of all behavioral weight loss intervention trials between 1990 and 2010 reporting separate results by ethnicity and sex. Across 25 studies, African-American women on average lost less weight via lifestyle interventions such as diet, exercise, and behavior management [32].

A small retrospective observational study of 41 patients after Roux-en-Y gastric bypass (RYGB) surgery found significant discrepancy in percent of excess weight loss (%EWL) between European and African Americans [33]. Six months post gastric bypass, patients with European background had a mean %EWL of 40.6 +/- 17.3, while the African Americans and Hispanic groups combined had a %EWL of 30.9 +/- 11.5 (p= 0.04). Importantly, that other variables, including age, gender, pre-surgery BMI, number/type of comorbidities or number of pre-surgery medications, impacted %EWL. A large study of 1,684 patients undergoing either RYGB or laparoscopic gastric banding (LAGB) also found similar racial discrepancies in %EWL with a longer follow-up, at 1, 2 and 3 years post-operatively [34]. The analysis of data from the ten hospitals in the Kaiser Permanente Southern California healthcare system found that African American patients lost 18% of starting body weight at 3 years post-surgery (including both RYGB and sleeve gastrectomy) compared to 22% for both European and Hispanic Americans [35]. Recognizing these disparities, a retrospective study of 415 patients with African and European backgrounds attempted to determine the contribution of modifiable and non-modifiable risk factors to %EWL at 1 year post-RYGB [36]. Whereas age and preoperative BMI were associated with lower %EWL, European ethnicity clearly predicted greater effects of treatment as compared to African Americans. Thus, whether the intervention is lifestyle or surgical African Americans tend to lose less weight than European Americans with similar treatments.

A line of possible interventions aimed to reduce racial disparities in obesity and type 2 diabetes is physical activity/exercise. Despite the known racial disparities in cardiometabolic diseases and the integral role of regular exercise in their prevention, it is noticed that there are only a few studies focused on determining which exercise protocols can best address racial differences in the physiological response to exercise. Multi-racial/multi-ethnic cohorts that assess physical activity often do not present the results related to physical activity by race [37-43]. However, multiple cross-sectional studies strongly suggest racial differences in the physiological response to exercise. The clear majority of these studies focus on vascular function. Although vascular health can be assessed using different methodologies, most frequently used method is flow-mediated dilation (FMD), which also provides an index of endothelial nitric oxide (NO)-dependent vasodilation [44]. NO is the principal molecule involved in regulation of vascular tone and hemodynamics. Several lines of evidence indicate that general vascular function and, more specifically, endothelial NO-dependent vasodilation is reduced in African Americans as compared to European Americans [45-48]. Even healthy African American participants demonstrate reduced FMD and NO-dependent vasodilation [45-47]. Consistently, this racial difference has been demonstrated in the participants with metabolic syndrome, suggesting that race may be an independent non-modifiable risk factor for vascular dysfunction. However, these decrements in FMD can be improved in African Americans with regular exercise training [48-53]. Six weeks of aerobic exercise training elicited improvements in vascular function and blood pressure in middle aged to older hypertensive (excluding stage II hypertension) African American participants as well as in pre- and post-menopausal women [50,53,54]. In addition, resistance training during 6 weeks also produced favorable effects on the vasculature [52]. Some *in vitro* data suggest that beneficial vascular effect produced by exercise might be enhanced in African Americans. For example, endothelial cells from African Americans as compared to European Americans, showed more pronounced increases in NO production in response to *in vitro* laminar shear stress (a model of exercise) [49]. These data collectively suggest that race-specific protocols may improve weight loss and cardiometabolic effects of life-style interventions and/or treatments in African Americans.

Systemic F_2-isoprostane levels as race-specific metabolic phenotype

We propose that race-specific interventions should be focused on non-invasive biomarkers of racial predisposition to obesity and type 2 diabetes. Our research identified lower levels of urinary F_2-isoporstaness among African Americans as an unfavorable metabolic chacteristic [25-27]. Here, we present evidence that urinary F_2-isoprostanes can serve as such non-invasive biomarker.

F_2-isoprostanes and risk of type 2 diabetes

In 2005, we published the results of a pilot case-control study nested in the Insulin Resistance and Atherosclerosis Study (IRAS), a multi-ethic cohort with approximately equal number of non-Hispanic Whites, Hispanic Whites and African Americans [55,56]. The IRAS was a prospective study and included two physical examinations determining diabetes status, e.g. in 1992-94 (baseline) and at 5-year follow-up in 1997-99. It has been hypothesized that elevated F_2-isoprostane levels – as biomarkers of oxidative stress – will predict increased risk of type 2 diabetes. This hypnosis was based on the overwhelmingly convincing but solely cross-sectional findings: participants with type 2 diabetes or its main risk factors showed elevated indices

of oxidative stress, including F$_2$-isoprostanes, as compared to unaffected individuals [3,57]. We aimed to determine whether elevated levels of oxidative stress markers precede the development of type 2 diabetes. In this pilot study, the abundant urinary 2,3-dinor-5,6-dihydro metabolite of iPF(2α)-III (F2-IsoPM) was used as a biomarker of oxidative stress. We compared baseline creatinine-corrected 2,3-dinor-5,6-dihydro-iPF(2α)-III levels between 26 cases (developed diabetes during follow-up) and 26 controls (remained free of diabetes). Surprisingly, elevated levels of urinary F$_2$-isoprostanes were found among controls. Even after taking into account the major diabetes risk factors, the adjusted odds ratio for the difference between the 75th/25th contrast was 0.32 (95% CI: 0.12, 0.81) [55]. This finding suggested that elevated F$_2$-isoprostanes are associated with reduced risk of diabetes.

Because our prospective finding contradicted the direction of the cross-sectional associations, we deemed that two confirmation studies are needed: first, to validate urinary F$_2$-isoprostanes as indices of oxidative stress in humans, and second, to expand the study to the entire IRAS cohort. We developed a new method to quantify four urinary F$_2$-isoproatane species simultaneously. The four isomers were carefully selected to represent (1) the most frequently measured isomer iPF2α-III, (2) its beta-oxidation metabolite with high urinary levels 2,3-dinor-iPF2α-III and (3.4) two F$_2$-IsoPs from the VI-series, iPF2α-VI and 8,12-iso-iPF2α-VI, as the most abundant in human urine [57-59]. In a clinical model of oxidative stress, doxorubicin-containing chemotherapy for newly diagnosed breast cancer was used as dosage-controlled oxidative assault [2]. In response to doxorubicin injection, levels of all four measured isomers of F$_2$-isoprotsanes increased in urine, demonstrating that these are valid indices of oxidative stress in humans [2]. Note, that other frequently used biomarkers of oxidative stress, plasma levels of malondialdehyde and protein carbonyls, showed no changes in response the systemic oxidative stress produced by chemotherapy [60]. Then these four F$_2$-isoporstanes, as validated indices of oxidative status, were used to determine the association with the risk of type 2 diabetes in the entire IRAS cohort [61]. Not only the inverse association between F$_2$-isoprostanes and incident diabetes was confirmed but new clues on what can underline this association were found. Specifically, these associations were especially pronounced among those with obesity at baseline, suggesting involvement of a metabolic characteristic underlying obesity-driven pathway to type 2 diabetes.

Urinary F2-isiprostanes and weight change

The next step in searching for the roots of the seemingly contradicting results from the cross-sectional and prospective studies was examining the associations between F$_2$-isoprostanes with BMI and weight changes [62]. As expected based on previously published results, the cross-sectional analysis of the baseline data showed direct association between four F2-isoprostane isomers and overall obesity (BMI ≥ 30) with the odds ratios ranging from 1.18 to 1.74 [3,57,63]. Similar, associations were found with abdominal obesity: the odds ratios ranged from 1.12 to 1.64. Clearly, 2,3-dinor-iPF(2α)-III showed the strongest associations with both definitions of obesity. Consistent with our results, a large study of Chinese

women found that urinary 2,3-dinor-5,6-dihydro-iPF(2α)-III, also a beta-oxidation metabolite of iPF(2α)-III, showed stronger cross-sectional associations with obesity as compared to the parent iPF(2α)-III [63,64]. It was important to confirm that our cross-sectional results do not contradict the consistent findings of this cross-sectional association.

The prospective analysis showed and inverse associations between baseline F2-isoprostane levels and for relative (≥ 5%) as well as absolute (≥ 5 kg) weight gain [62]. Similarly, to the cross-sectional analysis, 2,3-dinor-iPF(2α)-III showed the strongest inverse associations with weight gain: the odds ratios for the relative and absolute weight gain were 0.67 (95% CI: 0.47, 0.96) and 0.57 (95%CI, 0.37, 0.87), respectively. Thus, urinary excretion of beta-oxidation metabolites of iPF(2α)-III emerged as most sensitive F$_2$-isoprostane specie for the obesity-related metabolism. An independent study later confirmed the results demonstrating in a cohort of older adults demonstrating that higher levels of plasma F$_2$-isoprotanes were associated with weight loss [65].

Compensatory mechanisms can explain opposite direction of the cross-sectional and prospective associations between F$_2$-isoprostanes and obesity

The prospective findings of the inverse association between F$_2$-isoprostanes and weight gain and with the risk of type 2 diabetes are in direct contradiction to the epidemiological literature interpreting the cross-sectional association with BMI as obesity-induced oxidative stress [3,57,61,62,65]. This led us to hypothesize that systemic F$_2$-isoprostane levels reflect a compensatory mechanism [55]. We postulated that a compensatory mechanism involved in the maintenance of energy balance can explain the opposite direction of the cross-sectional and prospective associations between F$_2$-isoporstanes levels and the risks of obesity and type 2 diabetes [55]. Negative energy balance (weight loss) leads to a decrease in energy expenditure, whereas positive energy balance (weight gain) leads to an increase in energy expenditure [66]. With fat mass being the predominant element of body mass changes, fat oxidation plays an essential role in physiological control of energy balance [67-69]. Clearly, efficient fat oxidation in a non-obese person lowers the risk of weight gain and thereby, the risk of obesity and type 2 diabetes [70,71] (Figure 1). We hypothesized that urinary F$_2$-isoprostanes reflect the intensity of oxidative.

Mitochondrial Metabolism → ROS → F$_2$-isoprostanes: F$_2$-isoprotanes are produced by a non-enzymatic reaction between polyunsaturated fatty acids, mostly arachidonic acid, which is a ubiquitous part of biological membranes, and reactive oxygen species (ROS) [1,72]. Urinary F$_2$-isoprotanes reflect the overall ROS levels [2,5,72]. Mitochondrial oxidative metabolism – as the major endogenous source of ROS- is likely to be a significant contributor to systemic F$_2$-isoprotane levels. Given that skeletal muscles comprise the bulk of oxidative tissues, it is likely that skeletal muscles contribute significantly to systemic ROS levels and therefore, to systemic F$_2$-isoprotane levels [73-77].

Fat Utilization → ROS → F$_2$-isoprostanes: Fatty acid oxidation largely contributes to skeletal muscle metabolism
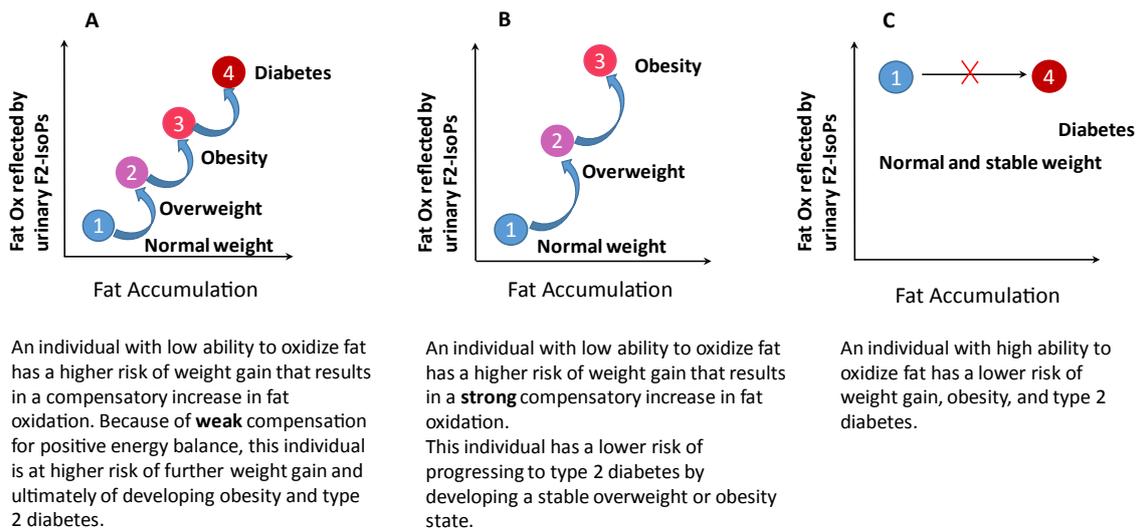
Figure 1: Proposed relationships between urinary F2-isoprostanes and fatty acid oxidation rates.

in the post-absorptive state and during physical activity [78-80]. Also, fatty acid oxidation generates (as compared to other substrates) enhanced ROS levels [81-84]. Thus, individual differences in urinary F_2-isoprostanes levels may reflect variability in fatty acid oxidation.

Several observations support these relationships. In the IRAS cohort, we found that urinary F_2-isoprostanes are directly associated with circulating fasting free fatty acids, which are known to intensify muscle fat oxidation [62]. Mean levels of four F_2-isoprotanes increase across the tertiles of free fatty acids distribution: at the highest tertile of free fatty acids (T3) F_2-isoprotane levels are 30%-36% greater as compared to the lowest tertile (T1), with p-values for the trend <0.05 [85]. In addition, we obtained evidence confirming the hypothesis that factors intensifying muscle fat oxidation reduce the risk of type 2 diabetes. We showed that fasting free fatty acids predict lower type 2 diabetes risk: OR=0.47, 95% CI, 0.27-0.81 in the IRAS cohort [85].

Metabolomics studies demonstrated shifts in circulating acylcarnitine levels associated with intensified fat oxidation, namely during fasting and moderate intensity exercise [86,87]. The fasting study demonstrated decline in circulating levels of C3, C4 and C5 (derivatives of amino acid oxidation), whereas C2 levels increased [86]. The moderate intensity exercise resulted in a transient increase of C8, C10 and C12 levels [87]. We developed a composite index of four urinary F_2-isoprostanes and examined the relationships between F_2-isoprostanes index and the above mentioned acylcarnitine. We found direct associations with C2 and C12 and inverse association with C5, which was consistent with our hypothesis [88].

Exercise → Protective Effect → Fat Utilization → F_2-isoprostanes: The most convincing evidence for our hypothesis is the well-accepted role of physical activity in protecting against obesity and type 2 diabetes [89,90]. Physical exercise undeniably increases mitochondrial metabolism, fatty acid oxidation, and concurrently, the levels of ROS and F_2-isoprostanes [74,77,78,91-93]. In our study, patients with non-small cell lung cancer were trained on an exercise bicycle for 14 weeks. Exercise training consisted of aerobic cycle ergometry sessions at 60 to ≥ 70% of baseline peak workload for 20–45 min

three days per week. Rest-time urinary samples were collected before the first exercise session (baseline) and at the end of the 14 weeks of training. In agreement with our hypothesis, urinary F_2-isoprostane levels increased with exercise training [94].

African ancestry is associated with low systemic F_2-isoprostane levels

Low mitochondrial metabolism and fat utilization have been found in African Americans and is thought as one of the metabolic factors underlying racial predisposition to obesity and type 2 diabetes [30,67,95-101]. We hypothesized that systemic F_2-isoprostane levels would be lower in African Americans as compared to non-Hispanic and Hispanic Whites [102]. Our results clearly indicated that urinary F_2-isoprostane levels are similar among the participants with normal BMI, but among the overweight and obese participants, African Americans had lower F_2-isoprostane levels. Based on our hypothesis, this finding suggests that increased adiposity in African Americans is associated with a weaker metabolic adaptation, i.e. smaller increases in fat oxidation in response to positive energy balance (Figure 1).

The most direct test of the hypothesized link between continent of ancestry ("race") and systemic F_2-isoprostane levels is a comparison of these biomarkers among three groups with *a priory* different proportion of African ancestry: non-Hispanic whites, US-born African Americans and African-born immigrants from West Africa. Self-reported African American race is associated with lower percentage of West African (83%) and a higher percentage of European ancestry (15%) as compared to West African immigrants (95% and 4%, respectively) [103]. We hypothesized that the metabolic characteristic determining low systemic F_2-isoprostane levels are more prevalent among West African immigrants as compared to African Americans and/or non-Hispanic Whites. The Study on Race, Stress and Hypertension (SRSH) included individuals 25-74 years old, self-identified as non-Hispanic Whites, African Americans or West African immigrants residing in Georgia and presented a unique opportunity to test this hypothesis [104]. In this study population, the most educated ethnic group was West African immigrants. Yet, the levels of plasma F_2-isoprostanes were lowest in West African immigrants (33.8 pg/ml), followed by

African Americans (51.1 pg/ml), and non-Hispanic Whites (80.1 pg/ml) [105]. When the study population was stratified by obesity status and morbidity, healthy non-obese West African immigrants had on approximately half as much mean levels of plasma F$_2$-isoprostanes as compared to non-Hispanic Whites (32.8 vs. 67.6 pg/ml). Healthy non-obese African Americans had 1.2-fold greater levels of plasma F$_2$-isoprostanes as compared to West African immigrants (40.6 vs. 32.8 pg/ml). Consistent with previously published studies, plasma F$_2$-isoprostane levels were greater among obese and increased with the number of chronic conditions, which presents the main basis for the argument that oxidative stress presents a mechanistic link between obesity and CVD risk [3,106,107]. In contrast, African ancestry, which is known to be associated with predisposition to obesity and type 2 diabetes, regardless of obesity and morbidity status was presented with lower plasma of F$_2$-isoprostane levels [105].

Based on these findings, we hypothesize that lower systemic levels of F$_2$-isoprostane among African Americans reflect an unfavorable metabolic phenotype (Figure 2). The importance of understanding the metabolic determinants of this phenotype is emphasized by a significant effort within the scientific community aimed to decrease systemic F$_2$-isoprostane levels via various interventions [108]. Our research suggests that systemic F$_2$-isoprostane levels present a modifiable favorable phenotype and can be used as non-invasive markers for the development of race-specific interventions targeting predisposition to metabolic conditions among African Americans.

To review published findings from other studies, we conducted a literature search using PubMed database and the following Medical Subject Headings 2017 (MeSH) terms: [(African Americans) AND F2 Isoprostanes]. This search identifies six studies, three of which describe the IRAS and the Study of Race, Stress and Hypertension (SRSH), the findings of which are summarized above. Additional three studies include pediatric population, a prospective multiethnic cohort of men followed for the risk of prostate cancer, and a small study that experimentally induced hyperlipidemia in 15 African Americans and 15 White Americans [102,104,105,109-111].

The small experimental study did not find differences baseline levels of plasma F$_2$-isoprostanes, the pediatric study included 82 African American children and 76 White American children and found no racial differences urinary F$_2$-isprostane levels [109]. This study also has not found the most consistent differences in urinary F$_2$-isprostane levels that have been confirmed in multiple study populations [1,3,4,62]. This discrepancy and the established changes in fat metabolism with age, and specifically, during puberty, complicate the comparison of pediatric and adults populations [112-114]. The cohort study of prostate cancer and the small experimental study did not report baseline levels of F$_2$-isoprotanes by race [110,111]. Thus, racial differences in systemic F$_2$-isoprostane levels present a potentially productive area of research, especially in relation to racial metabolic differences.

Potential for targeting F$_2$-isoprostanes by race-specific interventions

Similarly, to metabolic phenotype, systemic F$_2$-isoprostane levels are defined by both the genetic background and life-long exposures. Children with sickle cell disease are known to have hyperactive metabolism and have greater F$_2$-isoprostane levels [115,116]. Another well studied genetic condition Down syndrome presents with lower metabolic rate with a known predisposition to obesity [117]. We found that Down syndrome patients tend to have lower oxidative status, assessed by urinary allantoin (an oxidative modification of urate) and F$_2$-isoprostane levels [118]. At the same time, phenotypic plasticity of F$_2$-isoprostane levels can be most clearly presented by comparisons within genetically homogeneous populations. For example, the Danish study of monozygotic and dizygotic twins comprises in a relatively homogenous ethnic population [119]. Examining the heritability of urinary F$_2$-isoprostane levels, the Danish twin study found that only ~22% are defined by the genetic background [119]. Thus, systemic F$_2$-isoprostane levels reflect a metabolic characteristic that is flexible and can be targeted by lifestyle and/or pharmacological interventions.

The plasticity of mitochondrial metabolism and muscle fat utilization has been demonstrated by small studies showing
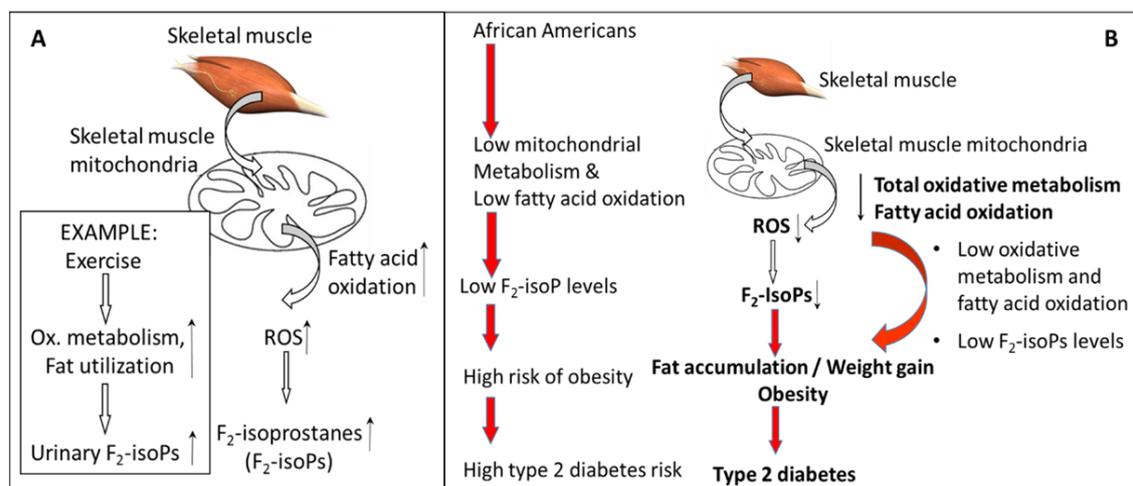
Figure 2: Physiological determinants of elevated metabolic risk associated with low F$_2$-isoprostane levels. (A) Hypothesized relationship between systemic F$_2$-isoprostane levels and skeletal muscle mitochondrial fatty acid oxidation; (B) Hypothesized relationship between skeletal muscle mitochondrial metabolism, systemic F$_2$-isoprostane levels and metabolic predisposition to obesity and type 2 diabetes in African Americans.

that these metabolic characteristics can be improved [30,120-122].Cortright et al. demonstrated that lean African American women have lower levels of muscle fat oxidation as compared to White women; yet the developed protocol of exercise training had a stronger effect on improving fat oxidation in the African American participants [30]. Pharmacological targeting fat utilization also may produce greater effects in African Americans. For example, metformin is known to increase fat oxidation [123-126]. Wlliams et al. demonstrated that metformin treatment produced a two times greater reduction in HbA1c in diabetic African American compared to White patients [127]. Thus, targeting fat utilization can be a productive basis for race-specific interventions aiming to reduce racial health disparities. Our research strongly suggests that systemic F_2-isoprostane levels, and specifically urinary F_2-isoprostanes, can serve as a simple, noninvasive means of assessing this metabolic characteristic over time and would be widely applicable in both the research and clinical setting.

The compensatory nature of the associations between F_2-isoprostanes and BMI predicts that weight loss will lead to reduction of F_2-isoprostane levels, which was demonstrated by Davi et al. [128] (Figure 1). This is in parallel with adaptive thermogenesis, that is, compensatory changes in energy expenditure and fat oxidation that favor fat mass homeostasis [129,130]. It is also known that metabolic response to weight perturbations differs between the individuals and is influenced by genetic background [131]. Such metabolic adaptation favoring homeostasis of fat mass is one of the central problems in maintenance of weight loss [132]. Based on the phenomenon of metabolic adaptation, greater F_2-isoprostanes levels should be interpreted as a favorable phenotype only in relation to body fat mass or BMI. Thus, F_2-isoprostanes in relation to BMI may provide the basis for targeted interventions to prevent obesity and type 2 diabetes among populations of African descent.

Conclusion

Conventionally, elevated F_2-isoprostanes levels are interpreted as indicators of harmful oxidative stress; and elevated F_2-isoprostanes in obesity are proposed as a mechanistic link between obesity and CVD risk [3,106,107]. Accordingly, significant effort is currently directed toward reduction of systemic F_2-isoprostanes levels via dietary changes and supplements [108]. However, an increasing body of evidence suggest a change the conceptual understanding of the role systemic F_2-isoprostanes play in human health, which may result in a shift opposite to the current direction – toward interventions aimed to increase systemic F_2-isoprostanes levels. As African Americans show lower systemic levels of F_2-isoprostanes, using these non-invasive biomarkers can enable the development of pharmacological and/or life style interventions targeted to the reduction of metabolic risks among African Americans.

Funding

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