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Journal of Endocrinology and Disorders
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Review Article

A Mini Review: Type 2 Diabetes Mellitus Reversibility in African American Adults

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Received Date: 28 February 2023 | Accepted Date: 11 March 2023 | Published Date: 20 March 2023

Citation: Yehayes B., Nwokike S., Odonkor W., Nunlee-Bland, G, Gambhir, Kanwal K, et al., (2023). A Mini Review: Type 2 Diabetes Mellitus Reversibility in African American Adults. *J. Endocrinology and Disorders.* 7(2): DOI:10.31579/2640-1045/129

Abstract

Type 2 Diabetes Mellitus occurs because of an over accumulation of excess fat in the liver from consumption of excessive amounts of food, especially carbohydrates, over a long period of time. This over accumulation of fat in the liver leads to the dysfunction of insulin, resulting in hyperinsulinemia. Additionally, the increased fatty acids in the liver leads to the excessive excretion of VLDL triglycerides and fat deposition in the pancreatic beta cell islets. As a result, there is diminished functionality of the pancreatic beta cells and decreased insulin sensitivity. However, this phenomenon can be reversed with adequate weight loss and result in remission the right behavioral and dietary modifications. The goal of this review is to explore the available literature and highlight the clinical findings that point to the reversal and remission of type 2 diabetes mellitus.

Key words: type 2 diabetes mellitus; African Americans; weight loss; insulin; obesity; diet modification; health disparities; social determinants of health; FFA

Introduction

According to the International Diabetes Federation (2021), there are approximately 567 million people living worldwide with diabetes and among them the overwhelming majority haveType 2 diabetes mellitus (T2DM) [28]. T2DM is a result of impaired insulin secretion by beta cells ofthe pancreas and tissue resistance to insulin resulting in dysfunction of glucose homeostasis, hyperglycemia and T2DM [19]. Impaired insulin secretion by beta cells of the pancreas is due to increased free fatty acids (FFA) from hyperlipidemia that deposit in the pancreas and cause chronic inflammation, stress on the islet's cells, and loss of islet functionality[12,55]. Similarly, tissue resistance to insulin is a result of increased counter regulatory hormones in the serum that mitigate insulin action, such ascatecholamines and glucocorticoids, as well as decreased insulin response in tissues, specificallyin skeletal muscle, hepatocytes, and adipose tissue [41,51].

Research also shows that fat accumulation in the liver is central to the pathology of T2DM. Increased calorie consumption over a long period of time results in more carbs being converted to fats in the liver via insulin stimulation. Fats decrease postprandial insulin secretion leading to increased fasting plasma glucose, insulin resistance, greater insulin levels overall, and greater conversion of carbohydrates to fats. These fats get exported to peripheral tissues and organs, such as the pancreas, causing further dysregulation of glucose homeostasis and T2DM [45].

High caloric diets rich in carbs and fats also lead to increased reactive oxygen species causing chronic low-grade inflammation [15,20]. The resulting release of proinflammatory molecules such as IL-6, IL-1, TNF-a, ALT, adiponectin, gamma-glutamyl transferase and CRP, are highly associated with an increased riskof T2DM, especially IL-1 which has been shown to activate nuclear factor kappa-light-chain- enhancer of B cells in the pancreas resulting in inhibition of their function and activation of apoptosis. Diets with high fat content can also induce increased liposaccharide production from gram negative bacteria in the gut contributing to metabolic inflammation [8].

The strongest risk factor leading to T2DM is obesity (Bellou et al., 2018), thus risk factors for obesity are associated with T2DM [4]. For example, a sedentary lifestyle leads to increased adiposity, which is associated with ectopic fat deposition into organs such as the liver,increased FFA leading to metabolic dysregulation, and inflammatory response [7]. In addition, reduced physical activity reduces blood flow into skeletal muscle resulting in decreased glucose uptake and hyperglycemia [48]. In contrast, increasing

physical activity is essential to prevent the development of T2DM because it increases anti- inflammatory molecules and reduces circulation of inflammatory molecules (Shamsuzzaman et al., 2004), and induces synthesis of antioxidants (Leeuwenburgh et al., 1994) as well as improving overall insulin sensitivity, glucose tolerance and lipid profiles [22,34,37].

Bellou et al., (2018) assessed the credibility of other non-genetic risk factors for the development of T2DM, and found that a low level of education and conscientiousness, smoking,air pollution and some medial conditions such as high systolic blood pressure, gestational diabetes, and preterm birth, had robust evidence for being associated with an increased risk of T2DM [4]. A low level of education is associated with a lower socioeconomic status which could also lead to poorer diets, increased stress, limited access to preventive care, unhealthy lifestyle patterns such as smoking, and living in unhealthy environments with increased air pollution which could lead to chronic inflammation. Furthermore, low conscientiousness could be correlated with decreased physical activity. Unfortunately, ethnic minority groups are more likely to experience these risk factors that whites in a higher socioeconomic status do not experience [52]. Moreover, minority groups are more likely to experience gestational diabetes, higher systolic blood pressure, and preterm birth, all of which have been found to be risk factors for T2DM [6].

With regards to genetic risk factors, Xue et al. (2018) found that there were 139 common variants of genetic loci and 4 rare variants that made a person more susceptible to T2DM [54]. Moreover, this correlation was unaffected after controlling for obesity and hyperlipidemia. They also found that rarer variants tended to have larger effects on T2D risk however these loci remain in the general population at low frequencies because of natural selection. Despite these findings, Catherine, Russell & Peter (2021) have noted that most studies on genetic factors leading to T2DM do not include subjects from different ethnic groups other than Caucasian populations, despite ethnic minority groups having higher rates of T2DM. For example, non-Hispanic blacks,Mexican Americans, and Native Americans have a T2DM prevalence rate 1.7 times, 2-5 times, and 2.8 times higher than non-Hispanic whites of a similar age respectively [18].

Despite the discrepancy in research, Cheng et al. (2012) did look specifically at African American ancestry as a risk factor for T2DM and their findings showed that the percentage of diabetic patients with African ancestry was greater compared to that of non-diabetic patients, even after adjusting for socioeconomic status (SES). Additionally, they identified two potential loci responsible for this risk at 12p13.31 (LOD=4.0) and 13q14.3(Z score=4.5, $P=6.6x10^{-6}$), however acknowledged that although genetic risk factors might contribute more than non-genetic risk factors, no single gene is responsible rather the interplay between genetic and non-genetic risk factors contributes to the increased risk of T2DM in African Americans. These findings echoed some researchers who postulated the “thrifty gene” hypothesis which states that populations that were subjected to repeated bouts of famine have developed a genetic predisposition to storage of fat. As a result, when these populations get exposed to Western diets,they are at increased risk for obesity and insulin resistance [3,40].

Although this hypothesis could explain why African Americans might have a higher genetic riskfor T2DM, it has been disputed [43].

In addition to African Americans having higher rates of T2DM compared to European Americans, they also have higher rates of diabetic complications and morbidity due to poor glycemic control. Studies have found that African American diabetic patients are less likely thanCaucasian Americans to have their glycosylated hemoglobin and lipids tested, as well as follow up ophthalmological visits [35]. Some have suggested this is because of the lower access to quality healthcare, but these health disparities persisted even after controlling for socioeconomic status and insurance coverage [5,17]. In conclusion, reversibility, and remission of T2DM independent of medications would have a significant impact in the African American patient population given the significant risk factors, lower quality healthcare, and poorer outcomes of T2DM.

Current research on the treatment of T2DM recommend a personalized approach based on medical factors such as comorbidities, glycemic level, and adverse reactions to medication and personal factors such as preference, age and social circumstances [53]. Initial treatment intervention involves lifestyle changes such as dietary modification, exercise, and adequate rest before the addition of medications to the treatment plan [35]. The first line medication in the absence of comorbidities, such as renal failure, hepatic diseases, acute heart failure and lactic acidosis, is typically metformin [36]. Metformin has proven to decrease fasting blood sugar levels by 20% and HbA1c by 1.5%. Its mechanism of action is blocking the mitochondrial enzyme glycerophosphate dehydrogenase (mGPD) which results in the reduction of hepatic gluconeogenesis and absorption of glucose in the intestine. This process leads to an improvement of peripheral insulin sensitivity, glucose uptake and glycolysis and leads to a reduction in LDL and an increase in HDL [36].Furthermore, other diabetic medications can be combined with metformin to achieve better baseline glycemic control [35]. For example, insulin therapy has proven to be effective in African American agents and can be used alone or combined with oral agents, such as metformin, however it is more likely to be utilized in patients who do not respond well to oral agents [2,35]. Ultimately, the recognized treatment for T2DM isan algorithm that contains a combination of lifestyle changes and medications.

Reversibility of T2DM

With the rise in cases of T2DM, the possibility of reversibility and remission is an exciting frontier in research. We define reversibility with regards to diabetes as complete stoppage of T2DM pathology and normalization to prediabetic levels. The underlying process occurs by a reduction of intra-organ fat deposition through the process of weight loss [44]. Taylor, Al-Mrabeh, & Sattar (2019) further elucidated that with calorie restriction, more fat would be utilized and less carbohydrates would be converted to fat [45]. Furthermore, intra-organdeposition of fats would decrease, and glucose homeostasis would normalize. They tested this hypothesis and found that within 7 days of a negative calorie balance, fasting glucose levels, liver fat levels, and hepatic insulin sensitivity normalized to the same level as non-diabetic matched control subjects. Furthermore, by 8 weeks they found that pancreatic fat content decreased. Moreover, no significant weight gain returned at 6 months of follow up of isocaloriceating after the initial 8-week period of acute weight loss, suggesting that T2DM can be reversed. These results also have significant implications for populations with increased susceptibility to fat storage such as African Americans.

Apart from diet modification, bariatric surgery also leads to reversibility of T2DM. The principles of bariatric surgery are similarly based on restriction and malabsorption, and result in rapid decreases of blood glucose and reversal of T2DM in 80% of patients in the short term [13]. Long term outcomes don’t depend only the surgery but other factors such aspatient lifestyle characteristics, comorbidities, and close monitoring [24].

Unfortunately, studies also show that African Americans have worse outcomes following bariatric surgery procedures, including major complications, re-admission, and mortality than non-African American patients [26]. As a result, bariatric surgery might not be asdesirable as lifestyle and dietary modifications and patients should be counseled as such.

Remission

The definition of remission with regards to T2DM has not yet been standardized. For example, to the *American Diabetes Association Journal*, the three criteria used to define remission are the occurrence of normoglycemia, the absence of the use of glucose-lowering therapy, and the maintenance of normoglycemia for at least one year [10]. Onthe other hand, the *UK Primary Care Diabetes Society and Association*, define remission as a fasting plasma glucose <7mmol/L or HbA1C <48mmol/mol on two

separate occasions and at least six months apart, weight loss, and attainment of glycemic parameters after total cessation ofall glucose therapies [37]. Regardless, studies show that remission is possible through primary care led dietary modification and weight loss maintenance [30]. Evidence points to remission for approximately 50% of participants in one 12-month study and approximately 33% participants in another 24-month study through dietary modification and weight loss management [23,31]. One study alsoshowed that African Americans were more likely to achieve remission after they followed 26 newly diagnosed non-Hispanic Black patients with T2DM for at least 1 year and found that > 40% of patients achieved remission as defined as near-normoglycemic control and recovery of beta-cells in glucose-stimulated insulin secretion (McFarlane, et al., 2001). Similarly, a robust study by Kaiser Permanente in Northern California (Karter, et al., 2014) revealed that African Americans are more likely to obtain remission in comparison to their white counterparts with an overall remission rate of 4.6% in seven years for individuals with T2DM [29]. They also found that sustenance of lifestyle modifications after weight loss results in a longer duration of remission and evidence points to remission for up to 5 years after intensive lifestyle modifications.

Several studies have shown that dietary restriction with low carbohydrate intake, such asthe Mediterranean diet, contributes significantly to weight loss and sustenance of weight loss of 8-12 kg for at least 2 years, a decrease in HbA1c, an increase in the rate of remission and a decline in the need for diabetic medications when compared to a low-fat diet (Esposito et al., 2014) [44]. Previously, dietary restrictions were focused on foods rich in fats and protein due to the known cardiovascular complications from a high fat diet and high kcal/g ratioof fats (9 kcal/g) and protein (4 kcal/g) [56]. However, recently dietary restrictions have been focused on carbohydrates to control postprandial glycemia [44].

Other examples of diets with a low glycemic index include proteinaceous foods such as legumes- beans, lentils, and peas [46]. In addition, research has shown tremendous benefits of incorporating an alkaline-ash diet to manage patients with T2DM. This isa diet is that consists mainly of fruits, vegetables, and milk with little to no red meat, fish, cereal, and dairy products. The alkaline- ash diet has proven to have beneficial effects in lowering blood sugar while providing better satiety for patients and reducing diabetic related complications [20]. In addition to macronutrient management to achieve weight loss and remission of T2DM, other dietary strategies that can be utilized is intermittent fasting which shows similar results to calorie restriction (Welton et al., 2020) or dividing single meals into smaller portions which has been found to result in increased satiety [39,50]. This can be useful in a buffet or snacking situation, where a person could take multiple small plates to split the food across or cut up the snacks and place them on different small plates.A person can also try dividing mealtimes up into several small courses, instead of putting everything on one plate. With these strategies they could lower their calories by reducing the sizeof their plate or how much food they put on it. Furthermore, Hughes et al., (2017) found that university students consistently put less food on a special portion control plate, which is a plate that has visual indicators for essential food groups, allowing people to adjust their portions without guessing [25]. Portion control plates are available in some stores. Over all these strategies canbe effective as patients that achieved greater than 10% weight loss after diagnosis were able to maintain remission for up to 5 years afterwards (Dambha-Miller et al., 2020), suggesting that moderate weight loss without drastic calorie restriction and intense lifestyle modifications are adequate to achieve remission [16]. Although the literature reveals promising results in terms of themagnitude of the effect of moderate weight loss on remission, more research should include a diverse patient population to better generalize the findings.

Apart from dietary changes, decreasing adipocytes through exercise can be a means of regulating insulin resistance. Comparing the effect of aerobic and resistance training has shown that aerobic exercise is more effective at regulating insulin resistance and associated inflammatory cytokines compared to resistance training and is also associated with a significant decline in Hba1C and improvement in insulin sensitivity [1]. From a molecular perspective, it has been proven that exercise increases the efficacy of the insulin sensitivity pathway by increasing molecular signaling of several post receptor signals involved in the insulin pathway, without necessarily affecting the gene expression (Iccarino, et al., 2021).

Other factors to consider include stress levels since increased stress stimulates production of glucocorticoid hormones that stimulate appetite resulting in weight gain [47]. Stress can also trigger emotional eating, which is when a person eats unhealthyfoods to try to control and improve their negative mood [14]. Additionally, patients those with low vitamin D blood levels are more likely to be obese and not likely to get enough exercise [49]. People can get vitamin D from the sun and some foods, such as egg yolks, fatty fish, certain mushrooms, and fortified foods [30].

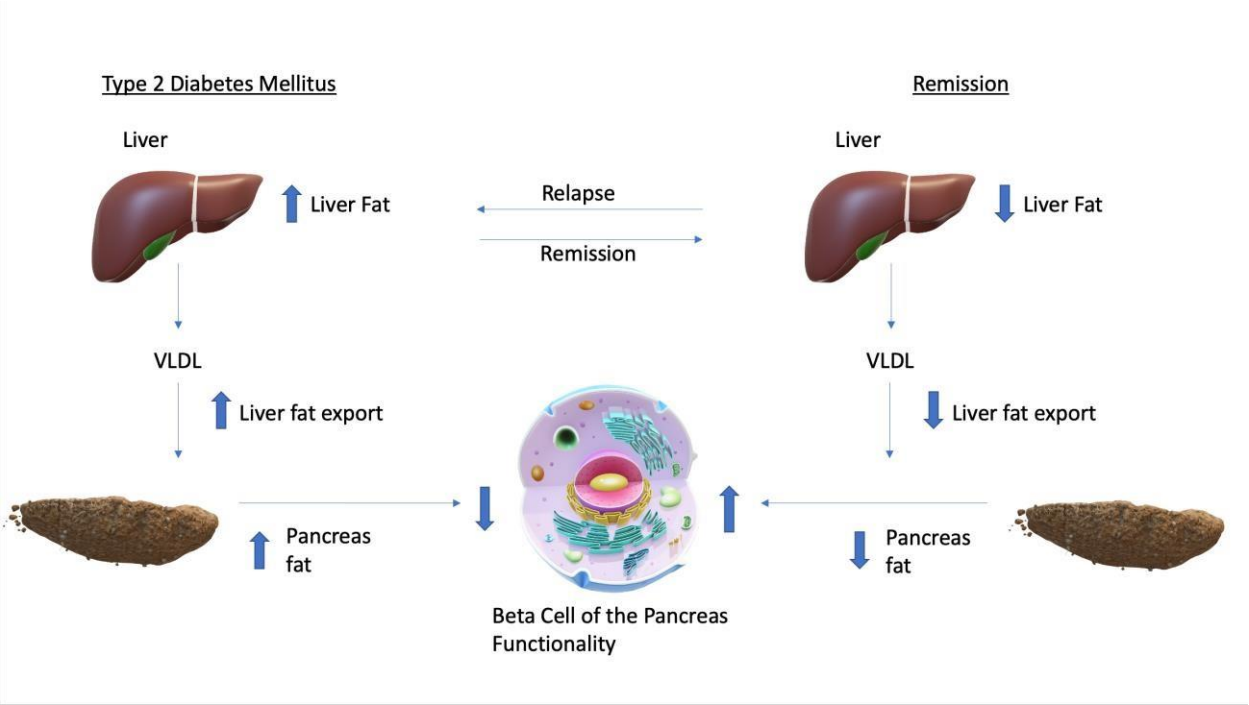

Figure 1: Pathophysiology of Type 2 Diabetes Mellitus and physiology of remission.

The pathophysiology of type 2 diabetes mellitus is a result of excess fat accumulation in the liver, in individuals with relative insulin resistance. As a result, there is increased VLDL exportation of fat to tissues of the body including the pancreatic islets which impairs insulin secretion and causes hyperglycemia. Eventually, the pancreatic islets will fail past the threshold for diabetes. The physiology of remission of diabetes occurs through the reduction of liver fat. As a result, there will be decreased VLDL export to beta cells of the pancreas which allows them to retain their functionality and continue toprevent the occurrence of postprandial hyperglycemia.

Conclusion

The reversibility of T2DM holds promising results for patients especially African Americans. However, due to the limited research on this topic and lack of diversity in patient subjects a lot is still unknown. The direction for future research should be centered on ethnically diverse populations, especially the minority groups because T2DM disproportionately affects them compared to Caucasians. Additionally, more research is needed to understand the genetic components of African Americans relating to their susceptibility to T2DM. As we await further research, education and more resources should be delivered to minority populations geared towards the prevention of T2DM through better lifestyle habits. Satvik meals (are light and healthy, most fresh fruits and vegetables, most whole grains, legumes, and nuts). How they are eaten, for example cooked versus raw, that provide longevity to life, enhance mode of goodness, purify one's existence and satisfaction. Such foods are juicy, fatty, wholesome, low in simple carbohydrates and rich in complex carbohydrates (roots like carrots, potatoes, radishes etc.).

Author Contributions

Kanwal K. Gambhir, Ph.D. conceived the idea and edited the drafts. First preliminary draft wasby D. Nwokike as a requirement of her senior elective MSIV. Final drafts were prepared by Dr.Yehayes as a requirement for his MSIV senior elective. Drs. M Fluitt, W. Odonkor, G Bland edited the final draft. All the authors agreed to contents of this manuscript.

Conflict of Interest Declaration:

All the authors declare no financial conflict of any sort for this manuscript.

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DOI: 10.31579/2640-1045/122