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Evaluating recent evidence from low carbohydrate diet in type 2 diabetes management: A systematic review and meta-analysis

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Abstract
Type 2 diabetes is epidemic worldwide and estimated to have affected about 415 million people today. The ideal dietary strategy for managing the diseases remains uncertain among researchers and health professionals. The objective of this review is to provide an overview of recent evidence while investigating the suitability and sustainability of low carbohydrate diets (foods containing approximately 50-130g of carbohydrate) in managing type 2 diabetes. A literature search was conducted considering randomised controlled trials (RCTs) of 6 months and above to explore the effect of low carbohydrate diet in treating type 2 diabetes with a meta-analysis. The mean difference for the changes in glycated haemoglobin (HbA1c) was used to measure treatment effects according to random effects analysis. Subgroup analysis by trial duration was conducted to discover the reason for the observed level of significance. The threshold for a statistical significance was $p<0.05$. Five studies consisting of 496 participants in total were included in the review. A meta-analysis of the various studies reviewed showed no significant change in HbA1c reduction (I^2 =0.0%, p =0.634), but saw a statistical significance in adherence to low carbohydrate diets (I^2=99.4%, $p<0.001$) signifying reduced energy intakes from carbohydrates. Subgroup analysis showed a significant reduction in HbA1c within 6 months. Overall, there was no significant difference in HbA1c in respective of good adherence to low carbohydrate diets. These findings are consistent with other meta-analyses which have shown good adherence to restricted carbohydrate and a short-term benefit of low-carbohydrates on glycemic index control.

Keywords: low-carbohydrate, type 2 diabetes, glycated haemoglobin (HbA1c)

Introduction

Diabetes mellitus is a chronic disease resulting from a complex metabolic disorder "that occurs when the pancreas is no longer able to make insulin or when the body can no longer make good use of the insulin it produces" [1]. This condition is usually characterised by constant hyperglycaemia (a chronically elevated blood glucose level) resulting from an absolute defect in insulin secretion, insulin action or both conditions [2]. The most common types of diabetes mellitus are type 1 diabetes mellitus (T1DM) which is insulin-dependent diabetes, previously known as juvenile-onset diabetes, and type 2 diabetes mellitus (T2DM) the maturity-onset/adult-onset diabetes and non-insulin dependent diabetes. Usually, T2DM accounts for about 90% of diabetes cases [1]. The progression of type 2 diabetes is an implication of abnormalities from insulin action or secretion and the endogenous output of glucose [3].

Another but less common type of diabetes is the gestational diabetes mellitus (GDM). According to the International diabetes Federation (IDF), it develops 1 in 25 pregnancies worldwide. Gestational diabetes gives rise to an increased blood glucose level that clears off after delivery. GDM may be a reflection of metabolic stress caused by the pregnancy [1].

The American Diabetes association has released some recommendations to serve as the standard of medical care in diabetes focussing on some aspects which include: self-management education, Nutrition, Physical activities, smoking cessation, psychological care, glycemic index control, diagnosis and treatment of vascular complications, immunization, intensification of insulin therapy in type 2 diabetes etc. [12]. Among other approaches in the management of type 2 diabetes; these include high protein diet, low carbohydrate diet, Mediterranean-style diet, low-fat diet, calorie-restricted diet among many others [13]. These various interventions on macro-nutrient modification in the management of type 2 diabetes have produced varying outcomes.

There is a need for research synthesis due to the exponential increase in medical research in recent times. This has motivated interest in various methods for synthesizing result from different studies. Among other statistical methods for analysis is the systematic review and meta-analysis of different studies in a research area [14]. This current review seeks to evaluate the evidence of low-carbohydrate diet from recent studies in the management of T2DM with use of a meta-analysis.

Some studies have recognised the short-term beneficial effects on the use of low-carbohydrate diets in the management of T2DM [4-5]. However, suitability and long-term effects are yet to be established. Only a few studies have lasted a trial period of 6 months and above [6-7].

There are inadequate long-term systematic reviews that compare the use of the restricted carbohydrate diets to other conventional diets in the management of T2DM [8].This review discussed type 2 diabetes focusing on glycemic index control (HbA1c) and assessing adherence to reduced percentage of energy intake from dietary carbohydrates as a compliance marker. The purpose of this investigation is to provide evidence-based recommendations for the application of low -carbohydrate diet as a dietary means of managing type 2 diabetes.

Prevalence of diabetes

Diabetes is a major global health challenge. Recent statistics from IDF (Intermediated Distribution Frame) estimated that about 415 million individuals are affected worldwide and this number is projected to increase to about 642 million by 2040 [1]. This growing epidemic situation has constituted a global burden threatening the health of people despite different lifestyle intervention measures experimented by researchers [9-10] and continuous updating of guideline recommendations from health bodies on how to treat or manage the disease [11-12]. An optimum control over diabetes is yet to be achieved.

Risks and complications of type 2 diabetes

Risk factors for T2DM are categorised under the non-modifiable (genetic) and modifiable risks which are environmental factors (obesity, physical inactivity) [2]. Fortunately, the manifestation of the disease from these modifiable factors could be prevented; however, both factors are important in developing T2DM [2]. T2DM is known to be associated with overweight (BMI greater than or equal to 25 kg/m^2) or obesity (BMI greater than or equal to 30 kg/m^2) [15], high blood pressure, dyslipidaemia, impaired glucose tolerance (IGT) etc. therefore known to have increased cardiovascular risk [1]. Physical inactivity and dietary factors are confounders to some of these risks and contribute more to overweight/obesity. T2DM is identified as a chronic illness in the UK and has been predicted by World Health Organization (WHO) to be the 7th leading cause of death by 2030 [16].

According to IDF consensus in 2009, men who have high waist circumference (WC) ≥ 94cm and women who had ≥ 80cm have high risk of health problems and even higher risks when waist circumference is found ≥ 102 cm and ≥ 88cm for men and women respectively [17]; implying that men have five times and women three times the likelihood of been diagnosed with obesity [11, 15].

T2DM is associated with long-term micro- and macro-vascular health complications leading to reduced quality of life and life expectancy [16]. Micro vascular complications affect over 80% of diabetic individuals and could occur as a result of hyperglycaemia and hypertension which can increase the risk of developing eye diseases (retinopathy), kidney diseases (nephropathy), pressure palsies, autonomic neuropathy, etc. [2] The risk of these complications could be reduced by a blood (glucose, pressure, lipids and hypertension) control, cessation of smoking among others [12]. The aforementioned are a few among the standards of medical care for diabetes recommended by the American Diabetes Association (ADA).Others include nutritional management, full involvement in physical activities, etc.

Blood glucose control is a major management approach to neurological and metabolic risks associated with diabetes [17]. It is measured by the percentage of glycated haemoglobin in the blood (HbA1c) which shows the mean glucose concentration in the blood for over an average of 8-12 weeks [18].

Life style intervention in approaches to diabetes management

There are some approaches to the general management of diabetes [17]. Consistent with [17], recently the National Institute for Health and Care Excellence (NICE) has given a list of recommended approaches to managing T2DM in adults to include individualised care, patient education, dietary advice, blood pressure management and blood glucose management (involving the use of drug treatment at some point), among others [19]. Treating T2DM involves a step by step approach, beginning with a change in lifestyle to include dietary modifications and increased daily physical activities [2]. This remains the foundational approach in managing T2DM before and when treatment may involve the use of oral anti-diabetic agents or at a later stage the use of injectable long-acting glucagon-like peptide-1 (GLP-1) receptor agonist or insulin [2].

Some dietary approaches experimented by researchers for diabetes management have carbohydrate restriction in common supposedly based on the principle of controlling insulin secretion which is triggered by carbohydrate intake and the theory of insulin resistance being a response to chronic hyperglycaemia and hyperinsulinaemia [20]. A common carbohydrate restricted diet is the Atkins diet [17]. Other dietary approaches exist in the management of T2DM. Health professionals continuously work towards providing suitable, safe and lasting dietary regimes for the management of T2DM. Despite some accomplished progress, a default diet for type 2 diabetes as suggested by Feinman and associates in 2008 [20] is yet to be established.

Carbohydrates are relevant to type 2 diabetes management because the condition develops over time due to insufficient insulin secretion and at the onset of insulin resistance in relationship to carbohydrate metabolism [2]. Although some researchers [21-22] suggest that the low carbohydrates have benefits in T2DM management, but the evidence are still not convincing [23]. Insulin being a metabolic hormone has major actions that affect the intermediate metabolism of glucose, lipids and proteins. The secretion is increased by raised nutrients (elevated glucose, amino acids), hormones, stimulations; adipokines etc. [2]. Therefore restricting carbohydrates in the presence of other factors affecting insulin action could be debatable.

Presently, there is no sufficient evidence to recommend the ideal amount of carbohydrates for individuals with type 2 diabetes [24]. The amount of carbohydrates needed to be consumed by a person will depend on several factors such as the gender, age, levels of physical activities and other intended goals such as loosing body weight or improving blood glucose levels [25].

The role of carbohydrates and the different types present in food

Carbohydrates when consumed are broken down to glucose which is an essential source of energy for effective functioning of the brain [26]. Carbohydrates according to Diabetes [25] have been categorised into various types such as starchy foods, sugars (naturally occurring sugar in whole fruits and free sugars added to foods like sweets) and fibre (insoluble fibre and soluble fibre). Fibres are non-digested and hence do not increase blood glucose levels. However, insoluble fibre such as found in whole meal bread and brown rice help to keep the digestive system healthy and research have found out that the soluble fibre such as found in oats, fruits and vegetables help to reduce blood cholesterol levels [25].

Low carbohydrate diet

Carbohydrates are one of the three major macronutrients in our diet which have sugars as their building blocks and are classified according to the units of sugars that combine to

make up one molecule [27].

Reviews by the Scientific Advisory Committee on Nutrition (SACN) on carbohydrates in 2014 have found no association between carbohydrate intakes and T2DM [28]. Based on this report, Public Health England (PHE) recommended the dietary reference value of total carbohydrate requirement for the population aged 2 years and above to be 50% of energy requirements. However, this figure varies among individuals [29].

Foods containing carbohydrate between 50-130g per 1000g are referred to as low carbohydrate diets [29]. An earlier research by Accurso and colleagues [30] established on the description from the American Diabetics Association (ADA) [31], also categorised daily carbohydrate intake into some brackets which they considered a suitable cut-off for the definition of low carbohydrate diets.

Low-carbohydrate diet (LCD): 10-26% of energy requirement (52.5 -136.5g of carbohydrate);

Moderate-carbohydrate diet (MCD): 26-45% of energy requirement (136.5 -236.25g of carbohydrate)

Low-carbohydrate ketogenic diet (LCKD) 10% of energy requirement (52.5g of carbohydrate).In estimate, 1gram = 16 kJ of carbohydrates [9].

Supported by another group of researchers [22] is a taxonomy which categorised carbohydrate diets into:

Very low-carbohydrate ketogenic diet (VLCKD): 20-50g/d or < 10% of the 2000 kcals/d diet;

Low-carbohydrate diet: <130g/d or <26% total energy

Moderate-carbohydrate diet: 130-230g/d or 26%-45%

High-carbohydrates: >230g/d or >45%.

As at 2010, the American dietary guidelines recommended 45%-65%of daily carbohydrate intake [22].

Carbohydrate metabolism and insulin action in diabetes

Carbohydrate metabolism is regulated by insulin and its counter-regulatory hormone glucagon at different stages under normal physiological conditions. Insulin stimulates glucose uptake by the insulin sensitive tissues through the glucose transporters (GLUT 1-4). GLUT 4 "insulin-regulated" has special relevant metabolic characteristics which make it responsible for the uptake of glucose into the skeletal muscles and adipose tissues and also for the passive movement of glucose from extracellular to intracellular spaces [2, 32-33]. During carbohydrate metabolism, the body's target is to sustain a tight control of glucose level in the blood stream, while having the excess stored as glycogen in the liver and muscles for periods of fasting/starvation [7] and other increased needs such as pregnancy and ill health. Hence, among other energy substrate circulating in the body, plasma glucose concentration is relatively constant (5 mmol/l) due to the coordinated control of glucose metabolism by insulin [32]. During periods of higher blood glucose concentration as a result of increased dietary carbohydrate intake, insulin stimulates glucose uptake through the GLUT 4 transporters, thereby inhibiting the release of non-esterified fatty acids from the adipose tissue and increasing glycogen synthase (glycogenesis), thus leading to a low concentration of fatty acids. There is a metabolic switch of the body to the use of glucose. However in the post-absorptive phase, as glucose concentration drops, there is a change in the insulin/glucagon ratio which stimulates the body to change from the use of glucose to fatty acids through fat oxidation, and an increased glycogen breakdown through glycogenolysis and gluconeogenesis thereby sparing glucose for the brain and erythrocytes which cannot use fatty acids [32].Conversely, the ability for the body to control blood glucose levels and the release of stored glucose from the liver is compromised by Diabetes [25]. In poorly controlled type 2 diabetes, there is an impaired insulin secretion and action through the pancreatic β-cell dysfunction and insulin resistance, thus leading to a perpetual elevated blood glucose and lipids concentration.

Methodology

Search strategy

This review comprises of recent studies in the last 11 years published from 2005 to May 2016. A systematic electronic search of English language published journal articles in PubMed-Medline was carried out to review low-carbohydrate diet and T2DM. The MeSH terms used were "carbohydrate-restricted diet" or "low carbohydrate diet" and "diabetes mellitus, type 2" or type 2 diabetes mellitus. Selection criteria included randomised control trials (RCTs) restricted to human studies and clinical trials, which evaluated low carbohydrate diets comparing them to other diets of higher percentage of carbohydrates intake on adult men and women (19+) with T2DM or obese patients with T2DM. The primary outcomes were HbA1c and weight loss.

Data Synthesis and Statistical Analysis

The effect size utilised in this study was the difference between the mean scores (baseline to post-intervention) of each endpoint of the intervention and control groups. Results for HbA1c, weight, energy intake from CHO were reported in percentages (%). However, one study by Gulbrand *et al.* [33] provided reports for HbA1c in % and mmol/mol; therefore, results from the other trials were directly converted to provide their corresponding figures in mmol/mol using the Diabetes UK monitoring and testing guide. However, since 2009, HbA1c has been measured and reported interchangeably in % and mmol/mol [18]. HbA1c efficiency outcomes were reported at baseline, 6, 12 and 24 months by Gulbrand *et al.* [33]; Yamada *et al.* [34] reported at baseline and 6 months. In contrast to the aforementioned, Iqbal *et al.* [35] and Davis *et al.* [36] only reported the mean change effects from baseline at 6, 12, and 24 months while Tay *et al.* [37] reported mean changes at 13 months which was the end of the trial. To get the mean change effects for [33-34], pre-intervention means were subtracted directly from post-intervention mean scores. One study [37] provided results in standards errors (SE), therefore to obtain standard deviation (SD), the equation in the Cochrane handbook [38] was followed: $SD = SE \sqrt{N}$

Similarly, results presented in confidence intervals [37] were equally converted to SD through the Cochrane handbook procedure.

{$SD\sqrt{N}$ x (upper limit – lower limit)/4.128(confidence interval on t-distribution)}

Hence, the results from studies included in this review were presented in mean and standard deviation. Meta-analyses were conducted with Stata 11 (Stata Corp, College Station, Texas), using a random-effects model. Studies were stratified by study duration.

Results

The electronic literature search identified 653 publications. However, many of the articles were discarded because they did not meet the inclusion criteria for this investigation. A

flow diagram explains and provides a visual representation of the selection procedure [Figure 1].

Outcomes from other characteristics based on randomisation, blinding procedure, primary and secondary outcomes, and loss to follow-up are explained by the Jaded scale and 0-1 marking scheme. [Table1]. The Jaded score for the included studies ranged between 3-4 points while the 0-1 marking scheme ranged between 4-4.5 points. All the included studies investigated participants with similar risk factors of overweight with T2DM, or obese with T2DM.

A meta-analysis of 5 publications [33-37] has shown no effect of low carbohydrate diet on HbA1c with an SMD (CI) of -0.09% (-0.30, 0.13). Current outcome from the various studies analysed obtained a statistically significant effect on reduction of energy intake from COH at $p < 0.001$ and 95% C.I of -4.09% (-10.42, 2.23) for a trial duration of up to 24 months. This result was widely affected by the study carried out by Tay and associates [37]. Overall, there was high heterogeneity for COH (I^2 = 99.4%, $p < 0.001$) but no evidence of heterogeneity on HbA1c (I^2 = 0.0%, p = 0.634) To further explore heterogeneity, a supplementary analysis was performed and stratified according to study duration of 6 months and 12-24 months. Subgroup analysis saw heterogeneity for COH in studies 12-24 months [33, 35-36] at I^2 = 99.4%, 95% CI -4.09 (-10.42, 2.23). One study was not analysed due to lack data on baseline intakes [34].

Adherence and attrition

Adherence and attrition rates from the included trials were assessed to review study compliance to the intake of reduced energy from low carbohydrate diets [Table 1].

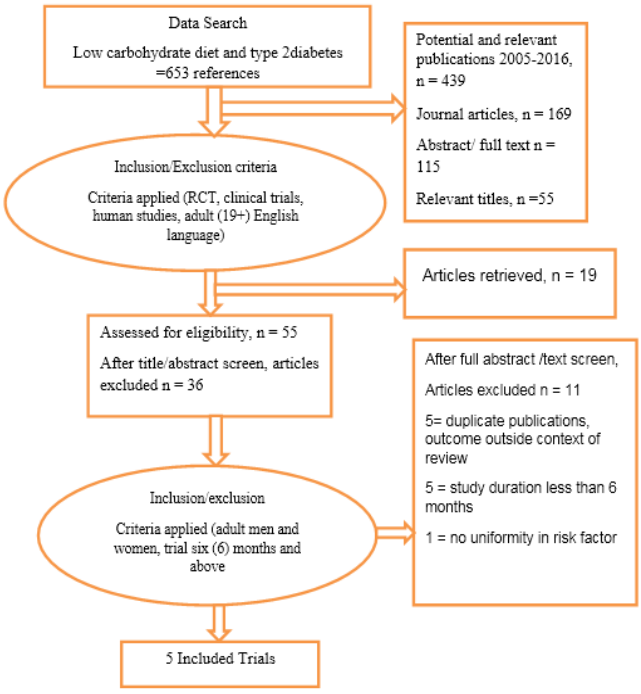

Fig 1: Study Flow Diagram

Discussion

This review of recent intervention studies analysed effects of low-carbohydrate diet on HbA1c inT2DMmanagement from trialswhich were compared to a control group. It agrees with other meta-analysis that although there may be greater short-term benefits of low carbohydrate diets onglycemic control,this outcome is not sustained over a long period.

Glycemic control

Blood glucose control is one of the major outcomes which are desired to be controlled through nutritional intervention in T2DM [22, 32]. Few studies [22, 36, &39] have reported beneficial outcome from low-carbohydrates on glycemic control. However, certain meta-analyses which have shown improved HbA1c from low-carbohydrates reviewed studies of shorter durations [37, 39]. This current analysis had extended the investigated duration from 6-24months to assess if there is evidence to recommend the suitability of the low-carbohydrate diet for blood glucose control in the long-term. Results from the various intervention studies analysed showed no significant effect [Table 2]. A justification for this outcome is obvious from the included studies. In the 6 months trial [34], non-calorie restricted low-carbohydrate diets were compared to a calorie restricted diet. There was an effect of -0.40(-1.21, 0.41). It was observed from another study [35] that similar results could be obtained in a typical outpatient living condition at 6 months -0.5(0.2) but the result was not sustained over time -0.1(0.2). Conversely, an intervention study by Davis *et al.* [36] yielded an average reduction of 0.12% within 3months which increased by 0.06% monthly from 3-12 months. Apart from the aforementioned studies, a 13 months trial was excluded from the analysis by STATA as there was no significant difference in HbA1c between intervention and control diet [Figure 2; Table 2].Conflicting to previous studies investigating low-carbohydrates [39], these findings suggest that the low-carbohydrate diets may have more beneficial effects on glycemic control within a short period but difficult to sustain over time. However, some studies have expressed some concerns about the health effects on the long-term administration of low carbohydrate diets on renal function, calcium metabolism, risk of cardiovascular diseases and hypoglycaemia associated with reduced carbohydrate intakes especially on people who undergo regimes of insulin or insulin secretagogues as reported in a recent review by Dyson [40].

Results from the current analysis are comparative with previous meta-analysis [13, 41] which found no significant effects in HbA1c and weight reduction from low-carbohydrates in a long term. A more recent meta-analysis on dietary carbohydrate restriction on people with type 2 diabetes [42] have shown that low carbohydrate diets have no greater benefits on the long term when compared to other dietary approaches. Apparently, there is no clear indication of the superiority of low carbohydrate diet to other dietary interventions in type 2 diabetes management. However, the low carbohydrate diets have evidence to prove efficiency and safety in the control of HbA1c and other cardiovascular risk in the short term as reviewed recently by Diabetes U.K [43]

Compliance to Low-Carbohydrate Diets

High carbohydrate diets are hypothesised to have a close association with overweight/obesity which is a risk factor for T2DM, but it is needful to remember that obesity is a multifaceted topic. Here, the compliance to energy intakes from low-carbohydrates in association with the comparative groups was assessed. For every nutritional intervention, there will be behavioural changes: it may be difficult for some people to change their traditional diets for an interventional diet [44]. Earlier studies [45] confirmed that subjects increased carbohydrate and caloric intake as the trial progressed, consequently indicating that there may be a challenge with sustaining any dietary interventions under low-intensity

treatments.

In contrast, the present analysis of intervention results saw a significant change in the percentage of low-carbohydrate intake from the various studies -4.09 (-10.42, 2.23**).** However, despite this result, low-carbohydrate diet showed not effect on HbA1c. Dietary adherence to any nutritional intervention is a major factor to the resultant outcomes. A possible reason for this effect may be as a result of the regular reminders that the subjects received via phone calls and text messages before each appointment schedule for the subjects [Table 1]. A number of outcomes varied within the studies, therefore, results from meta-analysis need careful interpretation. Three of the trials only had significant changes to low carbohydrate intake within 6 months but the participants increased their intakes subsequently. Although, previous meta-analysis suggested a greater adherence rates from low-carbohydrate diets group in the management of T2DM [22]. However, observations in the current studies are consistent with a trial which randomised 132 obese subjects to a low-carbohydrate or low-fat diet [46]. Without clear-cut evidence in support of low carbohydrate diets, it becomes a concern as to why the diet has been highly celebrated. There are evidences to show that the benefits observed from low carbohydrate diets could be equally attained from other dietary intervention approaches [40, 44].

This review has some limitations that are common to other systematic reviews: - a lack of predetermined percentage of carbohydrate to represent the low carbohydrate diets. As such the carbohydrates consumed by subjects varied in the different studies. Another limitation is the small number of included studies, hence the sub-group analysis where very few. For further studies, the inclusion of studies from other databases that this study did not include is suggested. Missing information and data from some of the studies limited the number of analysis that could be carried out, and lastly, most of the included studies had no mentioned form of blinding.

However, there are strengths that are worth appreciating from this work. These included studies that were all conducted using RCTs which is considered as the gold standard for clinical trials. This papers included trials had longer durations as against the shorter period common with previous meta-analyses as evident from an earlier review [46]. This study utilised two quality tests and all the included studies scored at least 3 or 4 out of 5 points from tests thus proving the high reliability of the studies. Like other systematic reviews, the results were comparedto other reviews to establish the similarities and variances.

Conclusion

Meta-analysis or recent trials showed no significant effect in HbA1c from low carbohydrates when compared to other diets in the management of T2DM. Stratification by study duration showed that there could be some improved glycemic control within the first 1 year; however, these results were not sustained. A good adherence to low carbohydrate diet which had no impact on glycemic control was observed. These outcomes suggest no convincing evidence so far to make the low carbohydrate diet a default diet in treating the T2DM. Until this era, low-carbohydrate diets have shown to be effective in controlling blood glucose concentration in T2DM. However, it has not outweighed the effect of other dietary approaches.Therefore, based on these findings, it is probably best for the population generalised approached on the use of controlled macro nutrients intake to be directed back to personalised nutrition involving the patients with their GPs and dieticians through strategies that will suit individuals culturally across all age groups based on individual choices. Diabetics UK have also recommended that for people who chose to follow a low-carbohydrate diet, blood glucose levels should be closely monitored with adjustment to medications to avoid the risks of hypoglycaemia. Moreover, regardless of either low-carbohydrates or not, patients are encouraged to choose healthier carbohydrates such as fruits, whole grains, pulses and cut down on the intakes of unhealthy carbohydrates such as those from refined sources (white rice, white bread), sugar and sugar sweetened beverages.

Also, the genetic predisposition and other possible existing health conditions of an individual plays a role on how the diet is metabolised in the system, these are factors that need to be considered before giving a universal conclusion on the ideal diet for the management of T2DM. These results could be used by researchers and other health bodies to redirect the use of nutritional intervention in managing diabetes.

References

1. International Diabetes Federatton. About Diabetes. [Online] Available from: URL: http://www. idf. org/ about-diabetes [Accessed 25th July 2016].
2. Holt RIG, Hanley NA. Essential Endocrinology and Diabetes. 6th ed. Chichester, Hoboken: Wiley-Blackwell. 2012; 168-175.
3. Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. The Journal of Clinical Investigation. 1999; 104(6):787-794.
4. Volek JS. Carbohydrate restriction improves the features of Metabolic Syndrome. Metabolic Syndrome may be defined by the response to carbohydrate restriction. Nutrition & metabolism. 2005; 2(1):31. https://www.diabetes.org.uk/About_us/What-we-say/Statistics/State-of-the-Nation-2016-Time-to-take-control-of-diabetes/
5. Daly ME, Paisey R, Millward BA, Eccles C, Williams K, Hammersley S, *et al.* Short-term effects of severe dietary carbohydrate-restriction advice in Type 2 diabetes--a randomized controlled trial. Diabetic medicine: a journal of the British Diabetic Association. 2006; 23(1):15-20.
6. Iqbal N, Vetter ML, Moore RH, Chittams JL, Dalton-Bakes CV, Dowd M, Williams-Smith C, Cardillo S, Wadden TA. Effects of a Low-intensity Intervention That Prescribed a Low-carbohydrate vs. a Low-fat Diet in Obese, Diabetic Participants. *Obesity.* 2010; 18(9):1733-1738.
7. Tay J, Luscombe-Marsh ND, Thompson CH, Noakes M, Buckley JD, Wittert GA, *et al.* Comparison of low-and high-carbohydrate diets for type 2 diabetes management: a randomized trial. The America Journal of Clinical Nutrition. 2015; 102(4):780-790.
8. Wyk HJ, Davis RE, Davies JS. A critical review of low-carbohydrate diets in people with Type 2 diabetes. *Diabetic Medicine.* 2016; 33(2):148-157.
9. Bhurji N, Javer J, Gasevic D, Khan NA. Improving management of type 2 diabetes in South Asian patients: a systematic review of intervention studies. BMJ Open. 2016; 6(4):e008986.

10. Coppell KJ, Kataoka M, Williams SM, Chisholm AW, Vorgers SM, Mann JI. Nutritional intervention in patients with type 2 diabetes who are hyperglycaemic despite optimised drug treatment—Lifestyle Over and Above Drugs in Diabetes (LOADD) study: randomised controlled trial. BMJ. 2010; 341:c3337.
11. Diabetes UK. State of the Nation 2016: Time to take Control of Diabetes, 2016. England: [Online] Available from: URL: https://www.diabetes.org.uk/About_us/What-we-say/Statistics/State-of-the-Nation-2016-Time-to-take-control-of-diabetes/ [Accessed 30th July 2016].
12. American Diabetes Association. Standards of Medical Care in Diabetes—2016. The Journal of Clinical and Applied Research and Education, 2016.
13. Ajala O, English P, Pinkney J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. American Journal of Clinical Nutrition. 2013; 97(3):505-516.
14. Moncrieff J. Research syntheis: Systematic review and meta-analysis. Journal of International review of psychiatry. 1998; 10(4):304-311.
15. World Health Organisation. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications; Report of a WHO Consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus. Geneva, 1999.
16. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. Plos med. 2006; 3(11):e442.
17. Nyenwe EA, Jerkins TW, Umpierrez GE, Kitabchi AE. Management of type 2 diabetes: evolving strategies for the treatment of patients with type 2 diabetes. Metabolism. 2011; 60(1):1-23.
18. Diabetes UK. Change in the measurement of HbA1c, 2009. URL: https://www.diabetes.org.uk/ABOUT_US/NEWS_LANDING_PAGE/CHANGE-IN-MEASUREMENT-OF-HBA1C/ [5th July 2016].
19. National Institute for Health and Care Excellence. Type 2 diabetes in adults: management. London: NICE Available from:URL:https://www.nice.org.uk/guidance/ng28/resources/type-2-diabetes-in-adults-management-1837338615493 [25th August].
20. Feinman RD, Volek JS. Carbohydrate restriction as the default treatment for type 2 diabetes and metabolic syndrome. Scandinavian Cardiovascular Journal. 2015; 42(4):256-263.
21. Hu T, Mills KT, Yao L, Demanelis K, Eloustaz M, Yancy JWS, Kelly TN, He J, Bazzano LA. Effects of low-carbohydrate diets versus low-fat diets on metabolic risk factors: a meta-analysis of randomized controlled clinical trials. American journal of epidemiology. 2012; 176 Suppl7(7):S44-S54.
22. Feinman RD, Pogozelski WK, Astrup A, Bernstein RK, Fine EJ, Westman EC, *et al.* Dietary carbohydrate restriction as the first approach in diabetes management: Critical review and evidence base. Nutrition. 2015; 31(1):1-13.
23. Tay J, Luscombe-Marsh ND, Thompson CH, Noakes M, Buckley JD, Wittert GA, *et al.* A very low-carbohydrate, low–saturated fat diet for type 2 diabetes management: a randomized trial. Diabetes Care. 2014; 37(11):2909-2918.
24. Yamada Y, Uchida J, Izumi H, Tsukamoto Y, Inoue G, Watanabe Y, *et al.* A non-calorie-restricted low-carbohydrate diet is effective as an alternative therapy for patients with type 2 diabetes. Internal medicine (Tokyo, Japan). 2014; 53(1):13-19.
25. Diabetes UK. Position statement low carbohydrate diet for people with diabetes, 2017. [On line] Available from: URL: https://www.diabetes.org.uk/Professionals/Diabetes-Update/ [Accessed 2nd August 2017
26. Mergenthaler P, Lindauer U, Dienenel GA, Meisel A. Sugar for the brain: the role of glucose in physiological and pathological brain function. *Trends Neurosci*. 2013; 36(10):587-97.
27. Don MacLaren, Morton J. Biochemistry for sport and exercise metabolism. Chichester: Wiley-Blackwell. 2013; pp. 128-130.
28. Scientific Advisory Committee on Nutrition. Carbohydrates and Health. London: TSO, 2015.
29. Public Health England. Adult obesity and type 2 Diabetes. United Kingdom, 2014. URL:https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/338934/Adult_obesity_and_type_2_diabetes_.pdf Public Health England
30. Accurso A, Bernstein RK, Dahlqvist A, Draznin B, Feinman RD, Fine EJ, *et al.* Dietary carbohydrate restriction in type 2 diabetes mellitus and metabolic syndrome: time for a critical appraisal. Nutrition & Metabolism. 2008; 5.
31. American Diabetes Association. Nutrition recommendations and interventions for diabetes. Diabetes Care. 2008; 31(Supplement 1):S61-S78.
32. Frayn KN. Metabolic Regulation: A Human Perspective. 3rd ed. Chichester; Oxford: Wiley-Blackwell, 2010.
33. Guldbrand H, Dizdar B, Bunjaku B, Lindström T, Bachrach-Lindström M, Fredrikson M, Östgren CJ, Nystrom F. In type 2 diabetes, randomisation to advice to follow a low-carbohydrate diet transiently improves glycaemic control compared with advice to follow a low-fat diet producing a similar weight loss. Diabetologia. 2012; 55:2118-2127.
34. Yamada Y, Uchida J, Izumi H, Tsukamoto Y, Inoue G, Watanabe Y, Irie J, Yamada S. A non-calorie-restricted low-carbohydrate diet is effective as an alternative therapy for patients with type 2 diabetes. Internal medicine (Tokyo, Japan). 2014; 53(1):13-19.
35. Iqbal N, Vetter ML, Moore RH, Chittams JL, Dalton-Bakes CV, Dowd M, *et al.* Effects of a Low-intensity Intervention That Prescribed a Low-carbohydrate vs. a Low-fat Diet in Obese, Diabetic Participants. Obesity. 2010; 18(9):1733-1738.
36. Davis NJ, Tomuta N, Schechter C, Isasi CR, Segal-Isaacson CJ, Stein D, *et al.* Comparative Study of the Effects of a 1-Year Dietary Intervention of a Low-Carbohydrate Diet Versus a Low-Fat Diet on Weight and Glycemic Control in Type 2 Diabetes. Diabetes Care. 2009; 32(7):1147-1152.
37. Tay J, Luscombe-Marsh ND, Thompson CH, Noakes M, Buckley JD, Wittert GA, *et al.* Comparison of low-and high-carbohydrate diets for type 2 diabetes management: a randomized trial. The American journal of clinical nutrition. 2015; 102(4):780-790.
38. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. Wiley Online Library, 2008.
39. Volek JS. Carbohydrate restriction improves the features of Metabolic Syndrome. Metabolic Syndrome may be defined by the response to carbohydrate restriction.

Nutrition & metabolism. 2005; 2(1):31. https://www.diabetes.org.uk/About_us/What-we-say/Statistics/State-of-the-Nation-2016-Time-to-take-control-of-diabetes/
40. Dyson P. Low carbohydrate diets and type 2 diabetes: what is the latest evidence?. Diabetes Therapy. 2015; 6(4):411-24.
41. Castaneda-Gonzalez LM, Bacardi Gascon M, Jiménez Cruz A. Effects of low carbohydrate diets on weight and glycemic control among type 2 diabetes individuals: a systemic review of RCT greater than 12 weeks. *Nutricion hospitalaria*. 2011; 26(6):1270-6.
42. Snorgaard O, Poulsen GM, Andersen HK, Astrup A. Systematic review and meta-analysis of dietary carbohydrate restriction in patients with type 2 diabetes. BMJ Open Diabetes Research and Care. 2017; 5(1):e000354.
43. Diabetes UK. Position Statement 2017: Low –carb diets for people with diabetes, 2017.: [Online] Available from: URL: https://www.diabetes.org.uk/professionals/position-statements-reports/food-nutrition-lifestyle/low-carb-diets-for-people-with-diabetes. Accessed 7th October 2018.
44. Emadian A, Andrews RC, England CY, Wallace V, Thompson JL. The effect of macronutrients on glycaemic control: a systematic review of dietary randomised controlled trials in overweight and obese adults with type 2 diabetes in which there was no difference in weight loss between treatment groups. British Journal of Nutrition. 2015; 114(10):1656-1666.
45. Westman EC, Yancy JWS, Mavropoulos JC, Marquart M, McDuffie JR. The effect of a low-carbohydrate, ketogenic diet versus a low-glycemic index diet on glycemic control in type 2 diabetes mellitus. Nutrition & metabolism. 2008; 5(1):36-36.
46. Kirk JK. Restricted-carbohydrate diets in patients with type 2 diabetes: a meta-analysis. J Am Diet Assoc. 2008; 108(1):91-100.
47. Diabetes UK. Position Statement 2017: Low –carb diets for people with diabetes, 2017: [Online] Available from: URL: https://www.diabetes. org.uk/professionals/ position-statements-reports/food-nutrition-lifestyle/low-carb-diets-for-people -with-diabetes. Accessed 7th October 2018.