

## Systematic Review

# A review of the significance of treating obesity and diabetes mellitus concurrently as a follow-up to our understanding of the disease

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## ABSTRACT

### Aim

With the growing epidemic of obesity in children, adolescents and adults globally, obesity has been found to be a risk factor for many non-communicable diseases like type 2 diabetes mellitus (T2DM), hypertension, dyslipidemias and many cancers. So much so that recently a term diabetes (Obesity and diabetes in the same patient, especially when the obesity had a causal influence on the diabetes) got introduced. The aim of this systematic review was to study how we can tackle together so that we can take care of the mortality caused by obesity and T2DM being responsible for more mortalities replacing malnutrition even in developing countries.

### Methods

We carried out a PubMed search, along with Excerpta Medica dataBASE (EMBASE)/Cochrane library, web sciences for the Medical Subject Headings (MeSH) Terms “obesity”, “diabetes mellitus (DM)”, “lifestyle including exercise”, “diet therapy for management of diabetes”, pharmacotherapy including foods rich in antidiabetics like anthocyanins”, “polyphenols”, “walnuts”, “monoterpenes” for same including “bariatric surgery (BS)”.

### Results

We found a total of 86,283 articles pertaining to obesity and DM together of which we selected 92 articles for this review after getting articles after searching cross references. No meta-analysis was done.

### Conclusion

Till date body mass index (BMI) is used to classify overweight and obesity. With decreased muscle mass being common in these obese patients it is important to measure the body composition. Further, one has to monitor body composition when getting the patient to lose weight. Importantly, the criterion used for labelling obesity also varies in different geographical areas in view of different phenotype of diabetes in South Asia. Weight loss can be achieved using lifestyle interventions like diet, exercise and importance of combining natural products from food in attaining weight loss along with controlling hyperglycemia utilizing pharmacotherapies obesity and T2DM, control. Bariatric Surgery (BS) remains the last resort for morbidly obese although it might have to be resorted in individuals where diabetes is resistant to medical treatment and be needed for those with BMI greater than 35 kg/m<sup>2</sup> or even less in case of resistant diabetics. Role of diets rich in walnuts, anthocyanins, soybean, chickpeas, curcumin, polyphenols and other vitamins and micronutrients including vitamin A, also needs to be considered while treating diabetes.

### Keywords

Diabetes; Diettherapy; Lifestyle; Body mass index (BMI); Exercise; Metformin; Liraglutide; Bariatric surgery (BS).

## INTRODUCTION

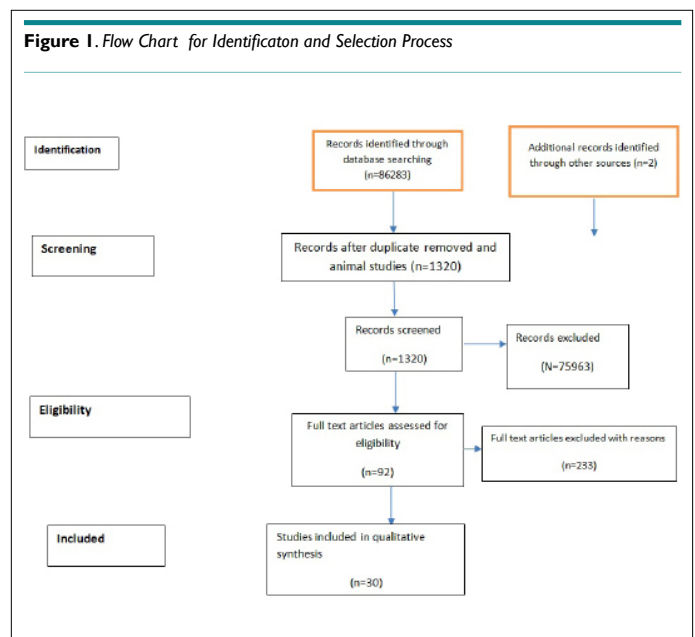
In the last century obesity has surfaced as the biggest global health problem in view of both, the changes in environment along with changes in society where positive energy balance and thus weight gain has resulted, main changes being consumption of high-calorie foods/high-fat foods, associated with inadequate physical activity, moving towards sedentary lifestyle.<sup>1</sup> As a result obesity prevalence practically doubled since 1980 all over the world, with world health organization (WHO) showing greater than 39% of adults greater than/equal to 18 year were overweight of which 13% were obese.<sup>2</sup> Additionally, a minimum of 41 million children below 5 years were overweight or obese.<sup>2</sup> Importantly severe obesity, a body mass index (BMI) greater than 35 kg/m<sup>2</sup> is becoming a part of this global epidemic, and that has severe bad effects on health, with increase in BMI implying increased mortality risk just like low BMI does.<sup>3</sup> However, now overweight or obese have become bigger killers in contrast to malnourished or underweight.<sup>2</sup> As per WHO overweight and obesity are the causative factors for 44% of type 2 diabetes mellitus (T2DM), resulting in 23% of ischemic heart disease patients and roughly 7-41% of some cancers.<sup>4,5</sup> Of these greatest association is of T2DM with obesity, with obesity related T2DM expected to double to 300 million by the year 2025.<sup>6</sup> Because of which the word diabetes got coined, suggesting that most patients with T2DM are obese.<sup>7,8</sup> The term diabetes highlights the etogenesis of effect of obesity on T2DM. This term was introduced by Shafir who saw that Israeli sand rats (*psammomys obesus*) fed high energy diets, became obese and later developed diabetes.<sup>9,10</sup> Thus, in concert they increase mortality risk of the individual by 7 fold.<sup>11</sup> This increasing trend gives an estimation of 60% of total population of the world to be overweight or obese by year 2030.<sup>12,13</sup> As per Zimmet T2DM is proving to be the greatest epidemic of mankind and has beaten all the figures and predictions given by WHO and intermediate distribution frame (IDF), with the numbers increasing to 415 million people and with these diabetics a population of a country can be formed like it is greater than 315 million people of US. Thus need to address diabetes together is there.<sup>14</sup> Since all antidiabetics are not weight neutral and antidiabetics being expensive there is a need to find non-pharmacological answers using diets which have phytochemicals, flavonoids and other pulses, walnuts in the low calorie diets which have inherent insulin resistant effects.

## METHODS

We carried out a PubMed search for the Medical Subject Headings (MeSH) terms “obesity”, “diabetes mellitus (DM)”, “exercise”, “dietary therapy” for management of diabetes, “pharmacotherapy”, “including natural products” which have antidiabetic properties like “walnuts some vitamins” and “minerals”, “anthocyanins”, “phenols for same including bariatric surgery (BS)”.

## RESULTS

We found a total of 86,283 articles pertaining to obesity and DM together of which we selected 92 articles for this review after retrieving articles after searching cross references. No meta-analysis was done (Figure 1).



### National and Asian Phenotypes

A sponsored study by Indian Council of Medical Research (ICMR) suggested the widespread, seriousness of diabetes across rural and urban areas with some areas showing prevalence as high as 13%.<sup>15</sup> Now evidence exists, that an “Asian phenotype” exists.<sup>16</sup> The Asian DM patient is characterized by onset at younger age, higher risk even at lower BMI, higher abdominal obesity, higher cardiovascular disease (CVD) in South Asia and stroke in East Asia.<sup>16</sup> Thus these typical characteristics need to influence the way treatment drugs are prescribed based on availability and selected in these geographical areas.<sup>17</sup>

### Role of History and Anthropometrics

Before starting the treatment of obesity it is important to consider if the patient has history of any disease for which patient is on any medications. For example if patient is on antidepressants like phenelzine, tranylcypromine, mirtazapine, or lithium, drugs known to cause moderate to significant weight gain<sup>18,19</sup> or antipsychotic agents like clozapine, olanzapine, risperidone, quetiapine<sup>20</sup>/or haloperidol again causing moderate to significant weight gain, or some antiepileptics like valproic acid,<sup>21-23</sup> carbamazepine,<sup>22-25</sup> gabapentin,<sup>26,27</sup> causing moderate to severe weight gain by increasing appetite and affecting metabolism, steroid hormones like prednisolone<sup>28,29</sup> or contraceptives like depot medroxyprogesterone acetate (DMPA),<sup>30</sup> some  $\beta$  adrenergic blockers like atenolol, propranolol, atenolol increase weight slowly by inducing fatigue and lower activity.<sup>31</sup> Hence, the importance lies in the physician realizing if one has to select any antidepressants he/she chooses SNRI's like duloxetine, venlafaxine, milnacipran that don't have weight gaining effects/or even minimal weight-lowering effects, of antipsychotics aripiprazole, ziprasidone having no effect to minimum weight gaining effects, and of antiepileptics choose topiramate or zonisamide in a patient who is slightly overweight or obese.

### Examination includin

Till date, BMI gets used to classify overweight and obesity though this does not take into account the persons body fat mass.<sup>32</sup> Although most people having a BMI >30 kg/m<sup>2</sup> are seen to have a >proportion of body fat it might be observed in roughly 1/3<sup>rd</sup> of individuals having normal weight also.<sup>33</sup> This incorrect fat-mass distribution occurs secondary to low muscle mass known as sarcopenia. Increased waist circumference (WC) can be used to identify these patients, with WC exceeding 80 cm in women and 94 cm in men of Caucasian origin.<sup>34</sup> In view of differences in ethnicities different cut-offs for different populations have been proposed,<sup>35</sup> like instead of upper limit of BMI of 25 kg/m<sup>2</sup> for normal BMI as per WHO, the suggested cut off for South Asians is 23 kg/m<sup>2</sup>, similarly for overweight 23-24.9 kg/m<sup>2</sup> as compared to 25-29.9 kg/m<sup>2</sup> in Caucasians and for obesity as per greater than 30 kg/m<sup>2</sup> for Caucasians, a value of 25 kg/m<sup>2</sup> id recommended in South Asians with a WC 90 cm and 80 cm respectively for men and women in contrast to 102 cm and 88 cm for Caucasians.<sup>35</sup> Independent of BMI, increased visceral fat distribution increases the risk of atherosclerosis along with mortality. This normally needs? for proper measuring a persons body composition say by dual energy X-Ray absorptiometry (DEXA), bioelectrical impedance analysis (BIA), BOD-POD, besides measuring WC. Despite drawbacks of these methods, they are important for monitoring the course of weight reduction along with changes in the respective body compartments.<sup>36,37</sup> Besides that what is important is to identify a cheap method to find the early stage of sarcopenia, in view of loss of muscle mass being common. For the elderly a questionnaire called SARC5-that has 5 questions as part, namely strength, assistance in walking, rising from a chair, stair climbing and falls. The global score of this questionnaire varies from 0-10 points, where each part gets a score of 0-2 points. A score of greater than/equal to 4 points predicts sarcopenia and hence warrants more detailed assessment in this aspect.<sup>38</sup> This SARC-F questionnaire is one of best tools regarding screening for sarcopenia, which in routine practice has already proved in late middle-aged and elderly.<sup>39,40</sup> In post BS patients to get detailed information on muscle function, hand-grip tests are used frequently.<sup>41</sup>

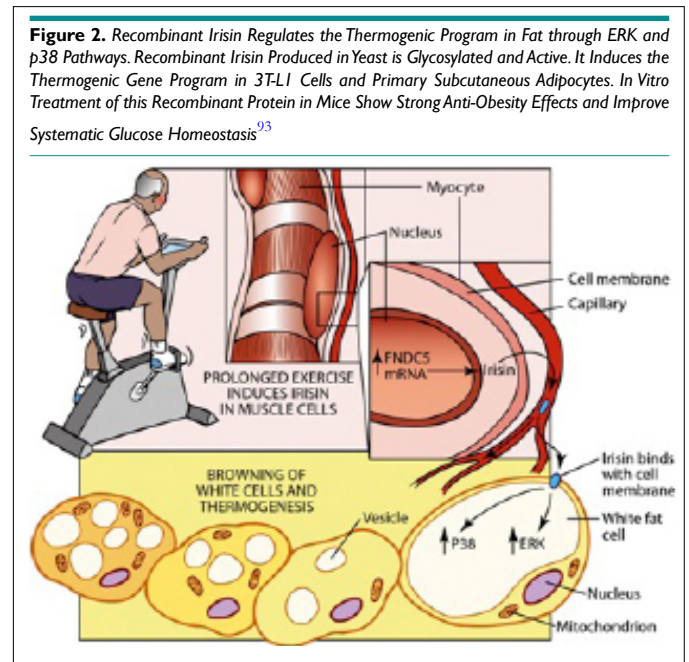
### Weight loss Methods in Obese and Overweight People

The main aim is to get weight loss. Various methods used include Life Style interventions which includes diet and exercise, use of antiobesity medications and BS.

### Life Style Interventions

**Role of Exercise:** Exercise is an important part of Life Style interventions. Aerobic exercise remains the best method for getting fat mass reduction. Other advantages an increase in lean mass, reduction in depression by release of endorphins, an improvement in glucose tolerance along with increasing insulin sensitivity, all by increasing irisin, and physical fitness (Figure 2). Because of which all scientific guidelines give a recommendation of at least 150 min/week of moderate aerobic exercise that needs to be combined 3 weekly times of resistance training for increasing muscle

strength.<sup>1,42-44</sup> Problem remains that these intensive Life Style interventions are difficult to follow along with maintenance over a long period of time, even if these patients get included in an optimal clinical trial as has been seen in the Look Ahead (Action for health in diabetes) trial.<sup>45</sup> Though exercise remains an integral part of weight loss obtainment, there have been different reports regarding additive weight loss when it gets combined the use of energy restricted diet.



**Figure 2.** Recombinant Irisin Regulates the Thermogenic Program in Fat through ERK and p38 Pathways. Recombinant Irisin Produced in Yeast is Glycosylated and Active. It Induces the Thermogenic Gene Program in 3T-L1 Cells and Primary Subcutaneous Adipocytes. In Vitro Treatment of this Recombinant Protein in Mice Show Strong Anti-Obesity Effects and Improve Systematic Glucose Homeostasis<sup>93</sup>

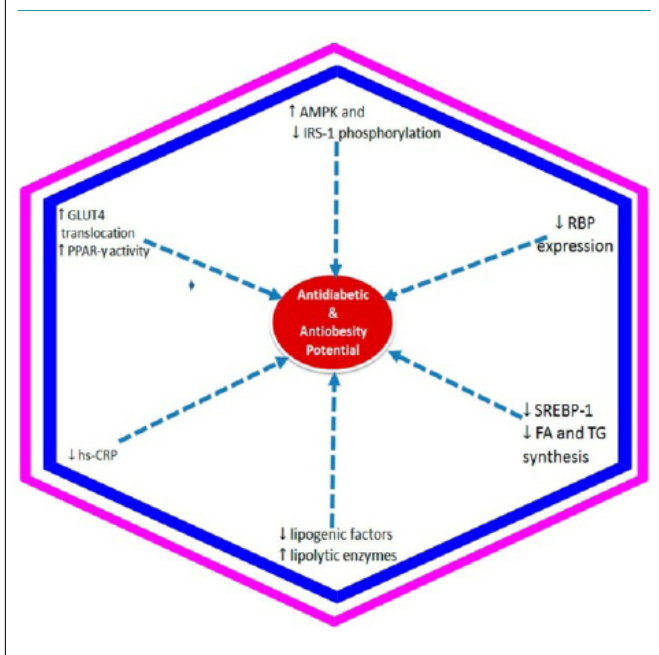
**Role of diet:** To get this a low fat, low carbohydrate, or the Mediterranean style diet can get used.<sup>46-48</sup> This Mediterranean style diet has advantages of better metabolic effects along with delaying need for delaying the antihyperglycaemic therapy in patients who had newly diagnosed T2DM.<sup>49</sup> Besides the mediterranean diet that might have these antihyperglycaemic effects, recently natural products have been introduced like anthocyanins which act through multiple mechanisms to increase insulin sensitivity in target organs like i) increasing Galacto-oligosaccharides that help in increasing glucose transporter 4 (GLUT4) translocation by increasing PPAR  $\gamma$  activity, ii) enhance activation of adenosine monophosphate-activated protein kinase (AMPK), along with downregulating serine phosphorylation pf insulin receptor substrate 1 (IRS-1) phosphorylation, iii) reduce the retinol binding protein (RBP) Expression and iv) lowering the highly sensitive C Reactive Protein (hs-CRP). Further weight reduction by anthocyanins is by mechanisms like reduction in sterol regulatory element binding protein-1 (SREBP1) mRNA levels and inhibition of fatty acid and triacylglycerol synthesis enzymes as well as down-regulation of lipogenic factors and upregulation of enzymes (Figure 3). Anthocyanins are present in berries which include blackberries, bilberries, chokeberries, elder berries, cranberries and raspberries that are the richest sources of anthocyanins. Many other highly colored fruits like strawberries, black currant, cherry, grape, coloured cabbage, eggplant and radish also have high levels of anthocyanins, thus it is important to include these in the low-calorie diets plans to improve insulin resistance (IR) along with helping in weight reduction.<sup>50</sup> Similarly importance of adding

soybeans, chickpea to this diet has shown to further improve IR by the bioactive compounds present in these, like anthocyanins, isoflavones, GLUT-4 levels, inhibiting adipogenesis by downregulating peroxisome proliferated-activated receptor- $\gamma$  (PPAR- $\gamma$ ), reducing adiposity, positively affecting adipokines, and increasing short-chain fatty acid producing beneficial bacteria in gut.<sup>51</sup> A low-fat diet must have adequate carbohydrates with complex carbohydrates instead of mono or disaccharides.<sup>52,53</sup> Although, what counts is maintenance of this diet regularly.<sup>54</sup> Hence in practical life it is to use wide type of diet options which suits the patients good preferences, Life Style along with the medical condition like in an Indian scenario patient using a vegetarian diet might like to consume these soybean, chickpeas and other pulses. Further replacing 1-2 meals/day by dietary supplements (low-calorie diets that have included aloe vera supplements, Habtemariam showed that the marketed supplements had benzoate derivatives along with methanol suggesting they don't meet the international aloe science council certification regulations)<sup>55</sup> might help in consuming very low calorie diet to maintain weight loss.<sup>56</sup> But this type of diet is not suitable for children, adolescents or elderly people.<sup>1</sup> In case of sarcopenia cases, one has to supplement exercise with high protein diet.<sup>57</sup> Time of protein intake and amino acid composition has been controversial.<sup>58</sup> In advanced age, all are important, like acquiring muscle mass, physical fitness along with overall physical activity.<sup>59,60</sup>

### Use of Weight Loss in Prevention of T2DM and Therapy

The pathogenesis of DM has been demonstrated to be a resistance to insulin action in peripheral tissue insulin is a major regulator of cell metabolism, which in addition, is also a growth factor. Insulin effects in target cells are mediated by the insulin receptor (IR), which is a transmembrane protein with enzymatic (tyrosine kinase) activity. However the IR, is represented by a heterogeneous family of proteins, which include 2 different IR isoforms (Exon 11 minus IR-A and exon 11plus IR-B), along with a hemireceptor of the cognate IGF-1 receptor. These different receptors may bind insulin and its analogs with different affinity and produce different biological effects. The main physiological role of the IR appears to be the metabolic regulation, whereas other receptor tyrosine kinases are engaged in regulating cell growth and/or differentiation. Receptor tyrosine kinases are allosterically required by their cognate ligands and function as dimers. In all cases but the IR (and 2 closely related receptors), these dimers are noncovalent, but the IRs are covalently maintained as functional dimers by disulfide bonds. It has been known for several years that many cancer cells require insulin for optimal in vitro growth. Recent data show i) that insulin stimulates growth mainly *via* its own receptor and not the IGF-1 receptor ii) in many cancer cells the IR is overexpressed and the A isoform, that has a predominant mitogenic effect, is more represented than the B isoform. These properties give a selective advantage to malignant cells when exposed to insulin. Because of these reasons, all conditions of hyperinsulinemia, both endogenous prediabetes, metabolic syndrome, obesity, type 2 diabetes before pancreatic exhaustion and polycystic ovary syndrome and exogenous (type 1 diabetes) to increase the risk of cancer. The complexity of the diseases associated with hyperinsulinemia and their therapies does not allow an exact evaluation of the cancer promoting effect of hyperinsulinemia, but its detrimental effect on cancer incidence and mortality is well-documented.<sup>61,62</sup>

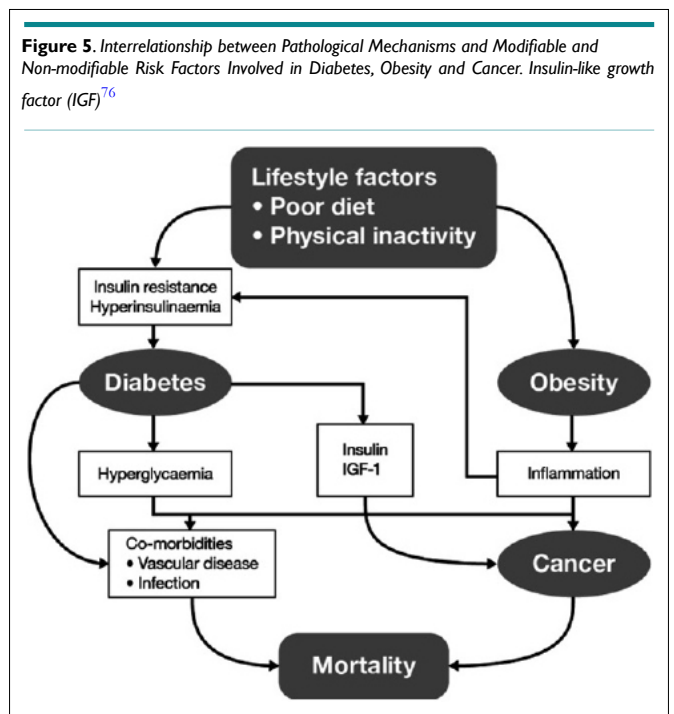
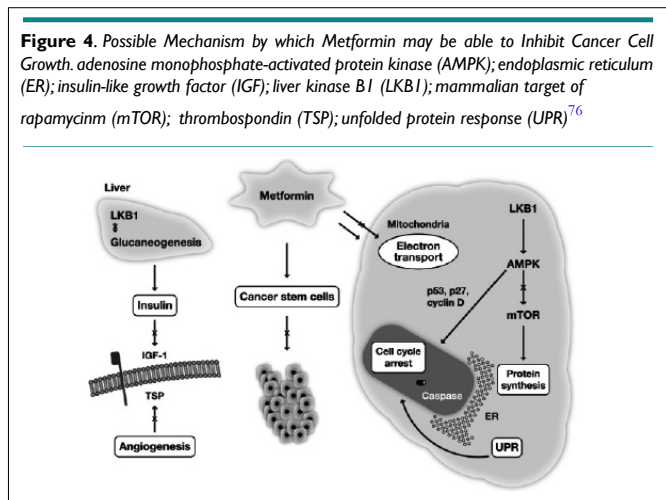
**Figure 3.** Underlying Mechanism of Anthocyanins Against Insulin Resistance Associated with Diabetes and/or Obesity. The Decrease in Insulin Resistance and Enhancement of Insulin Sensitivity by Anthocyanins in Target Organs have been Shown to be Mediated Through Activation of the adenosine monophosphate-activated protein kinase (AMPK) and Downregulated the Serine Phosphorylation of insulin receptor substrate 1 (IRS-1), Enhanced glucose transporter 4 (GLUT4) Translocation by Increasing the Activity of peroxisome proliferator activated receptor-gamma (PPAR- $\gamma$ ), Lowering the high sensitivity C reactive protein (hs-CRP) Concentration, and reduction of retinol binding 4 (RBP4) Expression. The Reduction of Weight Gain by Anthocyanins is also Reported Through Mechanisms Including Reduction in the sterol regulatory element-binding protein 1 (SREBP-1) mRNA Level and Inhibition of fatty acid (FA) and triglycerol (TG) Synthesis Enzymes as well as Downregulation of Lipogenic Factors and Upregulation of Lipolytic Enzymes<sup>50</sup>



Insulin resistance (IR) can be defined as a state in which greater than normal amounts of insulin are required to produce a biological response. Insulin acts by coupling to a cell transmembrane receptor, a tetrameric protein with 2 identical alpha subunits and other 2 beta units. Alpha subunits are extracellular and alter the insulin coupling translate the signal to both intracellular beta subunits which have tyrosine kinase activity and are autophosphorylated with a subsequent increase of their tyrosine kinase catalytic activity. Then endogenous protein substrates are phosphorylated and activate a cascade of intracellular signals which in turn induce migration of glucose transporter (GLUT-4) from intracellular pools to the cellular surface to facilitate glucose entry into the cell. So IR is due to an impairment of one or more of these steps of the process in target tissue which induce compensating hyperinsulinemia to maintain normoglycemia. But as years go by pancreas get exhausted and plasmatic glucose levels start to increase. Once glucose has increased, hyperglycemia has a toxic effect over islet cells (glucotoxicity) and has been demonstrated to impair the kinase function of insulin receptor (downregulation). An important consequence of IR is the increase in free fatty acids, which in turn impairs, even more, the IR (lipotoxicity). Even more IR on hepat-

ic, muscular and adipose tissue is associated with overproduction of proinflammatory cytokines, like interleukin6 (IL6) and tumor necrosis factor (TNF) and relative decrease of anti-inflammatory cytokines like adiponectin. All these factors contribute to chronic inflammatory status.<sup>63</sup>

With most T2DM patients being overweight or obese it is important to achieve weight loss for prevention of T2DM along with managing the disease once it occurs. As reviewed by farr OM and Mantzoros,<sup>64</sup> the Finnish Diabetes Prevention Study showed that an intensive dietary and exercise programme reduced the overall risk of T2DM by 58%.<sup>65</sup> similarly in diabetes prevention program, moderate weight loss with Life Style interventions in an obese population with impaired glucose tolerance test (GTT) could decrease the incidence of T2DM by 58%, though metformin use only reduced it by 31%.<sup>66</sup> Though the data for both strategies was not given in DPP. In another study with each 1 kg weight loss in the 1<sup>st</sup> year of DM diagnosis in T2DM was associated with 3-4 months increase in survival, with 10 kg loss associated with an increase in life expectancy by 35%.<sup>67</sup> For people having T2DM, it was demonstrated by Williamson DF et al that an intentional Weight loss of 10 kg as was seen in the American Cancer Society's Cancer Prevention study, total mortality got decreased by 25%.<sup>68</sup> Similarly the Look Ahead Study emphasized the improved weight loss that occurred in T2DM patients. As per this study even a 5-10% weight loss improved overall fitness, decreased use of antihyperglycaemic along with antihypertensive and lipid-lowering following 1 year.<sup>69,70</sup> On top of those depressive symptoms and the remission of obstructive sleep apnea or its decrease in severity resulted in secondary to weight loss.<sup>71,72</sup> But what was important was all these good effects needed a minimum of over 5% weight loss. With the need of intensive Life Style interventions, that includes energy restriction along with regular physical activity, getting this much Weight loss can't be the expected primary treatment outcome in real life for all overweight and obese patients. Still, there is need to encourage these patients to reduce energy intake, that might irrespective of their weight loss contribute to improve the glycemic control in them.<sup>73</sup> Consumption of walnuts have been approved for both T2DM prevention and maintenance of glycemic status.<sup>74,75</sup> One proposition is to consider weight loss medications for such cases which are suitable for these patients, giving a tug of war with their weight control.



Another important finding has been with diabetes, cancer risk increases, and addition of metformin reduces that risk<sup>76</sup> (Figures 4,5).

#### Trying Antiobesity and Anti Diabetes Therapy Together

The importance of properly controlling weight, improves body composition along with glycemic control was demonstrated by Olofsson E et al<sup>77</sup> where cardiovascular (CV), stroke along with mortality had a direct relation with weight gain during treatment with antidiabetics. Since many factors might influence these results hence it is difficult to prove a direct correlation of weight gain and morbidity, one can still say that weight gain indicates lesser therapy success and may potentially increase risk of mortality. With studying weight gain during antidiabetic therapies being not ethical still one should aim to use Antidiabetic agents that are weight neutral/help in weight reduction must be the 1<sup>st</sup> choice after the obligatory metformin therapy like alpha-glucosidase inhibitors, DPP IV inhibitors, SGLT inhibitors.<sup>78</sup>

Various antiobesity pharmacotherapy have been introduced worldwide. Of the new drugs reviewed earlier by us,<sup>79,80</sup> that are available in USA, only 2 of them were licensed for Europe like liraglutide (1.8 mg for T2DM, and 3 mg for treatment of obesity) along with contrave (a combination of naltrexone and bupropion) although not launched in many European countries and similarly not available in most developing countries like India. These drugs have shown to attain weight loss along with improving their Hb A1c levels.<sup>81</sup> Similarly semaglutide has shown improvement in weight control irrespective of BMI in SUSTAIN 1-5 Trials, examining once weekly semaglutide against placebo, sitagliptin, exenatide ER, Insulin glargine as add on to metformin/sulfonyl ureas, basal insulin trial.<sup>82</sup> Thus need to carry proper studies for finding the effect of antiobesity drugs in patients with T2DM is there.

## Role of Bariatric Surgery

BS has been proven to be effective for obese people having a BMI > 40 kg/m<sup>2</sup> or those with 35 kg/m<sup>2</sup> in the presence of T2DM or other comorbidities.<sup>83</sup> Of the most prevalent BS's available Roux-en-Y Gastric bypass and biliopancreatic diversions /duodenal switch surgeries are the most common and successful with initial reported excess weight reduction of upto 68-70%, where excess weight is the difference between total pre-operative weight and ideal weight.<sup>84</sup> Notably, improvement of glycaemic control by BS is rapid and often seen even before a clinically relevant weight loss. Despite intense scientific investigation, changes in metabolic rate or intestinal nutrients absorption do not explain the efficacy and sustainability of weight reduction.<sup>85</sup> Changes in food intake are frequently reported which are basically due to changes in food preferences, taste perception and modifications if central reward system.<sup>86,87</sup> In case of BS done in latter case remission was seen along with decrease in CV events in the Swedish Obese subjects study.<sup>88</sup> Currently, these surgeries are done even with lower BMI's. Problem with BS however, remains despite proper pre- and post-operative checkup long-term nutritional and micro nutritional deficiencies need lifelong vitamin and mineral supplementation. Further rapid and massive weight loss of muscle and fat-free mass may be greater than equal to malnutrition and osteoporosis. Thus need for follow-up regarding muscle and fat distribution as well as bone health is needed at least 2 years following surgery.<sup>89</sup>

## Bariatric Surgery and Drug Therapy Comparison

The surgical treatment and medications potentially eradicate diabetes efficiently 1 trial (STAMPEDE)-this 5 year trial supports the previous findings that BS is superior to intensive medical therapy in terms of glycemic control, weight reduction, decreasing medication use, (all therapies like antidiabetics, antihypertensives and lipid lowering agents) along with improving quality of life. All these effects were also seen in patients having milder obesity (BMI 27-34 kg/m<sup>2</sup>). This makes one consider that BS be also considered for these patients with T2DM with milder obesity.<sup>90</sup>

## Role of Vitamin A

Further role of vitamin A has been emphasized in both pathogenesis of obesity and diabetes, thus supplementation of vitamin A has been emphasized in both disorders.<sup>91</sup> Vitamin A is delivered by a specific protein called Retinol-binding proteins (RBP 4), which is emerging to have role of insulin resistance, the major cause of diabetes is highly associated with adipose tissue inflammation, and obesity. RBP4 interacts with 2 receptors, the Toll-like receptor 4 (TLR-4) and the plasma membrane protein is stimulated by retinoic acid 6 (STRA6), leading to the activation of c-Jun N terminal protein kinase (JNK) pathways and JAK2/STAT5 cascade respectively. Both mechanisms sustain IR. Hence ablation of STRA6 protects mice from RBP4 induced suppression of IR. Binding of retinol-bound retinol-binding protein to a membrane-binding protein suppresses insulin signaling. All-trans retinoic acid, a derivative of vitamin A, reverses these effects, resulting in increased insulin sensitivity, suppression of the *phosphoenolpyruvate carboxykinase*

(PEPCK) gene, and the induction of the glucokinase gene. Glucokinase and PEPCK are also regulated in opposite directions by the vitamin biotin, acting at the transcriptional level. Biotin also regulates the synthesis of insulin by the islet of Langerhans cells of the pancreas. The increase in advanced glycation end products (AGEs) is implicated in the initiation and progression of diabetes-associated microvascular diseases. Not only proteins in vitamin A, shuttle and signaling are emerging in diabetes, recently the discovery of 9 cis retinoic acid (9C RA) with effects on controlling glucose levels have opened a new scenario. Right now only pancreatic  $\beta$ -cells are able to show its synthesis, high-levels of 9C RA correlate with obesity.<sup>92,93</sup>

## CONCLUSION

Thus the importance of studying obesity and diabetes together is identifying the populations most specific for these by epidemiological studies as done by Zimmet in various regions of different countries and individualizing the anthropometric data for the geographic area and try to use weight neutral anti-diabetics like liraglutide if available, otherwise preferably SGLT2 inhibitors or DPP IV inhibitors not only improves the quality of life by preventing CVD, renal dysfunction, retinal function and improving life span, but also helps in preventing cancer if metformin is included in the antidiabetic regimen.<sup>76</sup> Further role of vitamin A has been emphasized in both pathogenesis of obesity and diabetes, thus supplementation of vitamin A has been emphasized in diabetes. Importance of using natural plants or fruits available products which have components acting as insulin sensitizers by acting on PPAR Gamma similar to thiazolidinediones, like anthocyanin, soyabean, chickpeas should be included in diet of diabetes patients along with walnuts. Also besides association of, T2DM, T1DM has also been seen associated with obesity, the incidence of which is increasing and can be taken care of by use of biguanides or GLP-agonists.<sup>94,95</sup>

## CONFLICTS OF INTEREST

The authors declare that they do not have any conflicts of interest.

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