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Weight Loss as an Integral Part of Obesity & Metabolic Syndrome Management

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Abstract: ***A 46-year-old female with type 2 diabetes mellitus for the last six years, works at bank, soccer mom with two children aged thirteen and eleven; reasonable diet. She does '' gym'' three times a week for thirty minutes. She wears an activity tracker; average step count approximately 4000 steps per day. She occasionally has back pain, legs and knee pain. Clinically Hight 160 cm; weight 84 kg; waist circumference 88 cm; Bp 140/85 mmHg; FPG 138 mg/dl; two-hour postprandial glucose 174 mg/dl; HA1c 7.8%; LDL–C 80 mg/dl; HDl-C 40mg/dl; BUN 21mmol/l; creatinine 1 mg/dl. Her current medication includes: gliclazide XR 60mg once daily; metformin SR1.5 grams daily; linagliptin 5 mg daily; telmisartan 80mg daily; rovsuvstatin 10 mg daily. How should this patient's condition be evaluated and treated? How would you further evaluated and treat this patient?***

Keywords: Type 2 diabetes; obesity; (BMI) body mass index; weight circumference

1. Introduction

Obesity is a chronic metabolic disease affecting people worldwide; which defined as body mass index more than 40kg/m2. It is a condition in which excess body fat has accumulated to such an extent that health may be negatively affected.It has been one of the leading causes of death, as obesity isthe main risk factor non-communicable diseases, including cardiovascular disease, type 2 diabetes, hypertension, coronary heart disease, arthritis, inflamed vein, cirrhosis, gallstones, pancreatitis, polycystic ovary, infertility, obstructive sleep apnea,certain types of cancers, diverse psychological problems or various physical disabilities. Until today the BMI is still used to classify overweight and obesity. [1-3] Body Mass Index (BMI) is a person's weight in kilograms divided by the square of height in meters. A high BMI can be an indicator of high body fatness. If your BMI is less than 18.5, it falls within the underweight range. If your BMI is 18.5 to <25, it falls within the normal. If your BMI is 25.0 to <30, it falls within the overweight range. If your BMI is 30.0 or higher, it falls within the obese range. [2,4,5]

Intra-abdominal fat deposition is linked to an increased risk for developing and cardiovascular disease compared with a more peripheralfatdistribution. The accurate measurement of intra- abdominal fat requires the use of advanced methods not available in clinical practice such as computed tomography (CT) or magnetic resonance imaging (MRI). On the other hand, a simple measurement of waist circumference is strongly correlated with risk for Demand cardiovascular disease. [6,7]

According to the National Cholesterol Education Program (NCEP), Adult Treatment Panel III (ATP III), and International Diabetes Federation (IDF), the increased waist circumference is one of the diagnostic criteria for the metabolic syndrome. [6,7] Metabolic syndrome is defined as a combination of factors that increase the risk of cardiovascular atherosclerotic diseases including diabetes, obesity, dyslipidemia, and high blood pressure. [8,9]

BMI possesses well-known limitations at the individual level, including the inability to directly distinguish between lean and fat tissue. Thus, at a given BMI, substantial variation in adiposity can occur. [10,11] Therefore, neither BMI nor waist circumference directly reflects the presence of underlying obesity related comorbidity.[12]

Recently, there is a new clinical staging system that ranks people with excess adiposity on a 5-point ordinal scale, while incorporating obesity-related comorbidities and functional status into the assessmentcalled: [13,14]

The Edmonton obesity staging system:
0. No apparent risk factors (e.g., blood pressure, serum lipid and fasting glucose levels within normal range), physical symptoms, psychopathology, functional limitations and/or impairment of well-being related to obesity.
1. Presence of obesity-related subclinical risk factors (e.g., borderline hypertension, impaired fasting glucose levels, elevated levels of liver enzymes), mild physical symptoms (e.g. dyspnea on moderate exertion, occasional aches and pains, fatigue), mild psychopathology, mild functional limitations and/or mild impairment of well-being.
2. Presence of established obesity-related chronic disease (e.g., hypertension, type 2 diabetes, sleep apnea, osteoarthritis), moderate limitations in activities of daily living and/or well-being.
3. Established end-organ damage such as myocardial infarction, heart failure, stroke, significant psychopathology, significant functional limitations and/or impairment of well-being.
4. Severe (potentially end-stage) disabilities from obesity-related chronic diseases, severe disabling psychopathology, severe functional limitations and/or severe impairment of well-being.

Worldwide obesity has nearly tripled since 1975. In 2016, more than 1.9 billion adults, 18 years and older, were overweight. Of these over 650 million were obese. 39% of adults aged 18 years and over were overweight in 2016, and 13% were obese. Most of the world's population live in

countries where overweight and obesity kills more people than underweight.[15]

A literature review was conducted to investigate the prevalence of metabolic syndrome in the Kingdom of Saudi Arabia. The review indicated a variance of metabolic syndrome between 13.6 and 57%. [16,17] This variation in prevalence is explained by the variation of targeted populations, age groups, gender, and the criteria used to define metabolic syndrome. It has been noticeable that the prevalence of metabolic syndrome is higher among females compared with males, and the increment was associated with aging. [17,18]

- **Effect of Obesity on Diabetes Mellitus Outcomes**

It is well established that patients with diabetes are at high risk of cardiovascular disease. [19-22]The association between obesity and the increased risk of cardiovascular disease is well established in the general population, in both men and women. [23-27] Overweight and obesity are highly prevalent among diabetic patients. [28,29]

The different approach to the relationship between obesity and disease, and in particular the relationship between excess adiposity andcardiovascular disease. Specifically, it is argued that (1) resistance to insulin action (and associated abnormalities) is the link between obesity andcardiovascular disease; and (2) overweight/ obese individuals differ in terms of their degree of insulin resistance and, therefore, their risk ofcardiovascular disease. [30-33]

It has been known for more than 30 years that obesity is associated with a decrease in Insulin-mediated glucose uptake.[34]

The relationship between obesity and insulin resistance remains controversial at several levels. Indeed, it is frequently assumed that obesity is essentially synonymous with insulin resistance and associated metabolic abnormalities. If this were not the case, it would be difficult to understand the genesis of the concept of a metabolically obese, normal-weight individual.[35]

If the obese individual is to be insulin resistant and metabolically abnormal and that these findings rarely occur in nonobese persons. The strongest evidence that insulin resistance is not a simple function of overweight/obesity comes from the report from the European Group for the Study of Insulin Resistance: the results of euglycemic, hyper insulinemic clamp studies in 1146 nondiabetic, normotensive volunteers showed that only approximately 25% of the obese volunteers were classified as being insulin resistant with the criteria used.[36]

In addition to understanding that insulin resistance, by itself and in the absence of its associated metabolic abnormalities, may not increase risk ofcardiovascular disease, it should also be understood that although insulin-resistant individuals are more likely to be glucose intolerant, dyslipidemic, and hypertensive, these abnormalities do not necessarily always develop. Thus, at a clinical level, it is more important to know whether the potential adverse consequences of being insulin resistant are present, rather than whether or not a given individual can be classified as being insulin resistant.[37]

- **Effect of Weight loss on Diabetes Mellitus Outcomes**

Observational studies have consistently associated obesity, physical inactivity, and low fitness with increased risk of cardiovascular disease. [38-40]

Randomized controlled trials have shown that lifestyle interventions to reduce weight and increase physical activity levels lead to diverse metabolic benefits, including decreased levels of insulin resistance, blood pressure, and inflammatory markers, improved lipid profiles, decreased incidence of type 2 diabetes, and among persons with diabetes, improved glycemic control. [41-46]However, whether these benefits lead to reducedcardiovascular disease incidence, which remains the greatest single cause of morbidity and mortality for adults with diabetes, remains unclear. Observational studies of intentional weight loss have yielded mixed findings, ranging from modest benefit to harm.[47]

The Look AHEAD Study (Action for Health in Diabetes), the largest randomized controlled trials to date of an intensive lifestyle-based weight loss intervention, led to numerous health benefits but had no significant effect oncardiovascular disease morbidity and mortality. [46,48-50] A variety of explanations have been offered for the lack of an effect of intensive weight loss intervention oncardiovascular diseaseoutcomes in Look AHEAD. One possible explanation is that the weight losses achieved were not large enough to produce an impact oncardiovascular diseaseoutcomes. Behavioral responses to intensive weight loss interventions are notoriously heterogeneous, as someparticipants have a limited weight loss or fitness effect in the first year, and others achieve substantial changes in weight or fitness. [51-53]

Modest weight loss through health-behavior modification can significantly prevent or delay the onset of type 2 diabetes in people at risk. Each kilogram of body weight loss is associated with a 16% relative reduction in diabetes risk [54]and a recent meta-analysis concluded that intentional weight loss of only ~5 kg is associated with a 15% reduction in all-cause mortality.[55]

- **Pharmacotherapies for Weight loss in Diabetes Mellitus &Bariatrics surgery**

Patients have access to many options including lifestyle modification, medications and surgery.Current literature has demonstrated that pharmacotherapy, exercise, and dietary changes have appositive effect on glycemic control and other diabetic indices. [56,57] There is moderate-strength evidence showed that participation in a comprehensive lifestyle intervention reduced the risk for type 2 diabetes in persons who are at increased risk. [43,58] There is low-strength evidence about the benefit of lifestyle intervention in prevention of all-cause mortality and insufficient-strength evidence aboutcardiovascular diseaseand microvascular outcomes in adults with diabetes.[46]

Anti-obesity drugs are approved in patients with a BMI ≥27kg/m2 with at least one obesity-related comorbidity such

as diabetes mellitus, hypertension, hyperlipidemia or sleep apnea or in patients with a BMI ≥30kg/m.The goal of treatment is not only to reduce weight, but more importantly to improve the comorbid conditions associated with obesity, such as hyperglycemia, hyperlipidemia, and heart disease.Currently, six major FDA-approved anti-obesity medications are available:[59]

- Orlistat: gastrointestinal lipase inhibitor; decreases intestinal energy absorption.
- Phentermine: noradrenergic, sympathomimetic amine; decreases appetite.
- Topiramate: decreases longer-term appetite and may have glycemic effects.
- Lorcaserin: selective 5-HT2C receptor agonist; increases satiety.
- Bupropion: thought to be dopaminergic and/or noradrenergic.
- Naltrexone: pure opioid antagonist. An opioid pathway is known that tries to stop or slow weight loss- naltrexone blocks this pathway.
- Liraglutide: glucagon-like peptide-1 receptor agonist (GLP-1 RA)
- Sodium glucose cotransporter 2 (SGLT2) receptor inhibitors (gliflozins) are a new class of potent antihyperglycemic agents that lower blood glucose levels and lower body weight as well as blood pressurein manner by increasing renal glucose excretion.[59]

Orlistat reduced progression to diabetes [60]and improved glycemic control in patients who already have diabetes [61] have also been noted. Fat malabsorption can give rise to side effects, including oily stools, faecal urgency and spotting if patients continue to consume a diet rich in fat, but these can be avoided with appropriate dietary restraint. Indeed, it is hypothesized that the effectiveness of orlistat likely reflects enforced dietary changes rather than a direct reduction in calorie absorption.[62]

The FDA approved a second anti-obesity agent for long-term use: a fixed dose combination of phentermine and topiramate extended release (marketed as Qsymia). Individually, these agents were already marketed for different indications and at higher doses, as a short-term adjunct for weight loss (phentermine) and for epilepsy and migraine (topiramate). As a centrally acting appetite suppressant with a mode of action similar to that of amphetamine.[63]Weight loss data for phentermine/topiramate are impressive, with a placebo-subtracted body weight reduction of 6.6 % at the approved dose of 7.5 mg phentermine/46 mg topiramate.[64] Modest reductions in systolic and diastolic blood pressure of 2.3 and 0.7 mmHg, respectively, were also observed. A higher dose of 15 mg phentermine/92 mg topiramate showed enhanced weight lowering of 9.3 % better than placebo,[65] but it is only recommended in selected patients who lose insufficient weight on the standard dose, because of increased adverse effects, including paranesthesia, dizziness, altered taste sensation, insomnia, constipation and xerostomia.[65]

Lorcaserin is a selective serotonin 2C (5-HT2C) receptor agonist in clinical development for weight management. The 5-HT2C receptor in the hypothalamus modulates food intake by activating the proopiomelanocortin system of neurons that induces hypophagia.[66]Lorcaserin significantly reduced body weight. In 4- and 12-wk randomized, double-blind, placebo-controlled studies, significant dose-responsive and progressive weight loss was observed at doses of 10 and 15 mg once daily and 10 mg twice daily. [67]

In a large two year trial incorporating background lifestyle modification in which patients taking lorcaserin 10 mg twice dailylost significantly more weight than placebo treated patients after one year of treatment and maintained more weight loss during year two.[68]In the Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) trial, a two-year, randomized, placebo-controlled, double-blind clinical trial shows lorcaserin used in conjunction with behavioral modification was associated with significant weight loss and improved maintenance of weight loss.Lorcaserin was also associated with improved values for biomarkers that may be predictors of future cardiovascular events, including lipid levels, insulin resistance, levels of inflammatory markers, and blood pressure.[68] Previously available drugs that targeted this receptor, such as fenfluramine and dexfenfluramine, were effective in promoting weight loss. However, these agents were nonselective, and as a result of 5-HT2B receptor activation, some patients developed valvular heart disease; these drugs were subsequently withdrawn from the market.[69]

Liraglutide is the first of the GLP-1 is an endogenous incretin, released by intestinal L cells in response to nutrient ingestion, which enhances glucose-stimulated insulin release by pancreatic B-cells and acts on satiety pathways, including hypothalamic POMC neurons, to reduce food intake.[70,71] Several analogues of GLP-1 are already marketed for type 2 diabetes.[72]A higher dose of liraglutide (3 mg, versus 1.8 mg for type 2 diabetes) led to treatment-related weight loss of 6 % over placebo.[73]As expected from its pharmacology, significant improvements in glycemic control for patients with type 2 diabetes were noted (0.9 % reduction in HbA1c), associated with improvements in measures of both B-cell function and insulin resistance. Like other GLP-1 agents,[72, 73]liraglutide increases heart rate, an observation that has not been satisfactorily explained, but evidence suggests it is not associated with an increase in arrhythmias or hypertension. There is a question of whether GLP-1- can increase the risk of pancreatitis has debatable. [74-77] Furthermore, Saxenda, like other GLP-1 receptor agonists, carries a boxed warning regarding a possible risk of medullary thyroid cancer. This stems from preclinical studies in which an excess of medullary thyroid cancer and C cell hyperplasia was noted in rodents; to date, there has been no evidence suggesting this is also a human phenomenon.[78]

The present 56-week randomized; double-blind, placebo-controlled trial examined the efficacy of liraglutide for maintaining prior weight loss achieved with a low-calorie diet. Liraglutide, an analog of the incretin hormone glucagon-like peptide-1, is currently approved for the treatment of type 2 diabetes at 1.2 or 1.8 mg per day (once-daily subcutaneous injection).[79]In patients with type 2 diabetes, treatment with liraglutide 1.8 mg per day over 26 weeks resulted in weight losses up to 2.6 kg greater than placebo.[80]In obese individuals without type 2 diabetes,

treatment with liraglutide 3.0 mg per day over 20 weeks resulted in a 4.4 kg greater mean weight loss than placebo and a 3.0 kg greater weight loss than orlistat.[81]Weight losses with liraglutide were sustained for up to 2 years with continued use of the medication.[82]In phase 3 randomized, controlled trial demonstrates the efficacy of liraglutide 3.0 mg per day, combined with lifestyle modification, in facilitating the maintenance of clinically meaningful weight loss. Liraglutide, compared with placebo, improved weight maintenance and induced additional reductions in cardiovascular disease risk factors, including waist circumference, fasting sugar, systolic blood pressure andhigh-sensitivity C-reactive protein.[83]

A number of GLP-1 receptor agonists have become availableinclude the short-acting agents exenatide twice daily,[84] intermediate acting liraglutide (administered once daily),[85] and the long-acting agents administered once weekly, including exenatide once weekly,[86] albiglutide,[87]and dulaglutide.[88]

Lixisenatide (administered once daily) has also recently been approved in the United States.[89] Short-acting GLP-1 receptor agonists have been reported to significantly reduce postprandial glucose concentrations, which is presumed to be secondary to effects on inhibition of gastric emptying. [90-92] Up to now, longer-acting GLP-1 receptor agonists with increased continuity of action have shown a more pronounced effect on fasting glucose than have shorter-acting drugs, mediated through insulinotropic and glucagon staticactions. [93-95]

Study findings have shown superiority of the once-weekly GLP-1 receptor agonists exenatide and dulaglutide (Eli Lilly, Indianapolis, IN, USA), to twice-daily exenatide.[96]

However, in head-to-head non-inferiority trials, the two approved once-weekly GLP-1 receptor agonists (exenatide and albiglutide;GlaxoSmithKline, Wilmington, DE, USA) have not shown non-inferiority to once-daily liraglutide.[97,98]Findings from long-term phase 3 trials showed that once-weekly dulaglutide 1·5 mg had better reduction of glycated hemoglobin (HbA1c) than did metformin, sitagliptin, and exenatide twice daily, with small weight loss and a safety and tolerability profile that is consistent with the GLP-1 receptor agonist class. [97,99,100]Dulaglutide has also been shown to have significant, sustained effects on both fasting and postprandial glucose concentrations. [97,99,100]

The AWARD-6 study lend support to the efficacy of the GLP-1 receptor agonist drugs dulaglutide and liraglutide for control of hyperglycemia in type 2 diabetes. With once-weekly dulaglutide 1·5 mg, patients administered substantially fewer injections and yet still achieved similar glycemic benefits. Long-term, once-weekly drugs might improve compliance compared with more frequently administered regimens, but this notion will require further assessment.[101]

Sodium glucose co-transporter type 2 (SGLT2) inhibitors, such as dapagliflozin, canagliflozin, and empagliflozin, decrease renal glucose reabsorption, which results in enhanced urinary glucose excretion and subsequent reductions in plasma glucose and glycosylated hemoglobin concentrations. Modest reductions in body weight and blood pressure have also been observed following treatment with SGLT2 inhibitors. SGLT2 inhibitors appear to be generally well tolerated, and have been used safely when given as monotherapy or in combination with other oral anti-diabetes agents and insulin. The risk of hypoglycemia is low with SGLT2 inhibitors. Typical adverse events appear to be related to the presence of glucose in the urine, namely genital mycotic infection and lower urinary tract infection, and are more often observed in women than in men.[102]Evidence from several reviews of the clinical literature suggests that SGLT-2 inhibitors improve glycemic control while also offering a favorable weight profile and a low risk of hypoglycemia. [103-107]

Liraglutide and SGLT-2 inhibitors have been compared against each other in head-to-head trials and shows liraglutide appears to offer better glycemic control in terms of lowering HbA1c levels, FPG, and achieving HbA1c targets in comparison to SGLT-2 inhibitors. Further, no weight-related consequences associated with the use of liraglutide over the use of SGLT-2s were observed. Overall, liraglutide has been demonstrated as an efficacious treatment option compared to SGLT-2 inhibitors in the management of people with type 2 diabetes. [108]

The combination of a GLP-1 agonist and an SGLT2-inhibitor has additive effects on lowering HbA1c and systolic blood pressure, body weight and cardiac risk and has the potential to synergistically reduce cardiovascular events and decelerate renal decompensation.[109]

There are several gastrointestinal operations including:

- Adjustable gastric band (restrictive), an inflatable band is used to create a small pouch, which limits food consumption and decease weight of about 15-20%.
- Roux-en-y gastric bypass (restrictive &malabsorptive), creates a smaller stomach and bypasses part of the intestine; results in increase GLP-1 (satiety hormone) which decease weight of about 27-33%.
- Vertical sleeve gastrectomy (restrictive), permanently removes most of the stomach, leaving a sleeve-shaped pouch; results in decease ghrelin (hunger hormones) which decease weight of about 25-30%.
- Biliopancreatic diversion (restrictive &malabsorptive), similar to Roux-en-y. A variant called a duodenal switch retains the pyloric valve, which decease weight of about 34%. [110-113]

The emergence of a large body of literature supporting surgical treatment of diabetes has led the International Diabetes Federation [114]andAmerican Diabetes Association [115]to recognize bariatric surgery as an effective treatment option for obese patients with type 2 diabetes.A meta-analysis by Buchwald et al,[116] reported an overall remission rate of 78% among diabetic patients undergoing bariatric surgery and similar remission rates for studies reporting outcomes less than two years and more than two years after surgery (80% and 75%, respectively). Currently, though, there are relatively few studies reporting long-term (more than five years) diabetes remission rates substantiated by

biochemical data.[117] Bariatric surgery can induce a significant and sustainable remission and improvement of type 2 diabetes and other metabolic risk factors in severely obese patients. The criteria for type 2 diabetes cure was met in 27% of gastric bypass patients. Surgical intervention within five years of diagnosis is associated with a high rate of long-term remission.[117]

Observational studies [118-122]and randomized, controlled trials, which have generally been short term studies, [123-135]have shown that bariatric surgery, when used specifically to treat diabetes, significantly improves glycemic control and reduces cardiovascular risk factors.[125-127]Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial, reported that, at one year and three years after randomization, both gastric bypass and sleeve gastrectomy were superior to intensive medical therapy alone in achieving excellent glycemic control (i.e., glycated hemoglobin ≤6.0%), reducing cardiovascular risk, improving quality of life, and decreasing medication use.[123-124]The five 5-year follow-up of patients in our trial showed that the beneficial effects of bariatric surgery on glycemic control were durable, even among patients with mild obesity (BMI of 27 to 34), which led to a sustained reduction in the use of diabetes and cardiovascular medications. Changes in body weight, lipid levels, and quality of life after surgery were superior to the changes observed after medical therapy alone. The potential benefits of bariatric surgery on clinical end points, such as myocardial infarction, stroke, renal failure, blindness, and death, as suggested in nonrandomized trials, can be adequately assessed only through larger, multicenter trials.[136]

2. Conclusion

Obesity is highly prevalent disease associated with increased morbidity and mortality. A full spectrum of care is essential to optimal treat obesity and metabolic syndrome. Treatment composed of diet modification, increased physical activity, utilizing weight loss medication as well as endoscopic therapy and surgical producers in appropriate patients.Surgery clearly has a role in morbid obesity. New understanding about obesity and metabolic syndrome management are treat weight first then comorbidities.

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