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Lifestyle Modification Is the First Line Treatment for Type 2 Diabetes

Kazuko Masuo

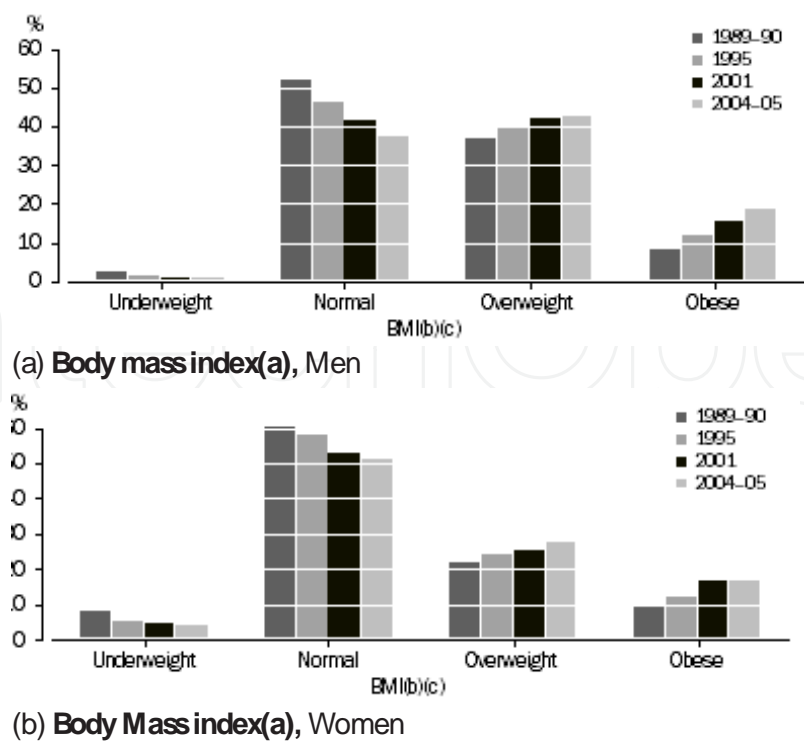
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1. Introduction

The prevalence of diabetes, especially type 2 diabetes and hypertension are significantly increased with the prevalence of obesity (Figures 1, 2 and 3) [1, 2]. Type 2 diabetes, hypertension frequently associated with type 2 diabetes, and obesity are important risk factors for cardiovascular morbidity and mortality and cardiac- and renal complications. Hyperglycemia as well as hyperinsulinemia in type 2 diabetes is a cardiovascular risk by itself [3]. Type 2 diabetes, hypertension and obesity are characterized by stimulation of the renin-angiotensin-aldosterone system (RAAS), elevated sympathetic activity and insulin resistance. Importantly, these characteristics, themselves, are one of the cardiovascular risks. Therefore, pharmacological and non-pharmacological treatments for type 2 diabetes should be selected from favourable effects on stimulated RAAS, elevated sympathetic nervous system activity, insulin resistance and leptin resistance.

Weight loss is recommended to delay and prevent type 2 diabetes in obesity, and for the treatment. Lifestyle modification such as a caloric restricted diet, reducing sedentary behaviour and an increase in exercise form the basis of all therapy. Weight loss treated with lifestyle modification including calorie restriction and/or exercise causes normalization of stimulated RAAS, sympathetic activation, insulin resistance, and hyperleptinemia, which are usually observed in type 2 diabetes and obesity. Recently, Straznicky *et al.* [4] and Masuo *et al.* [5] have shown the low caloric diet and exercise have different effects on insulin resistance, the RAAS, and sympathetic nervous activity in obese hypertensive subjects, although similar weight loss was observed between both interventions. Straznicky *et al.* [4] reported that exercise had stronger effects of normalized the RAAS stimulation, sympathetic activation and insulin resistance compared to diet only, whereas Masuo *et al.* [5] showed mild calorie restriction and mild exercise has different mechanisms on weight loss (normalization on sympathetic



Source: National Health Survey, Australian Bureau of Statics in 2008.
Prevalence of overweight and obesity has increased in both genders.

Figure 1. Overweight/obesity has increased in both genders in Australia [Source. Australian Bureau of Statics. 4819.0. Released at 11:30 AM (CANBERRA TIME) 25/01/2008] Reference [1]

activation for mild calorie restriction, and normalization on insulin resistance for exercise). The observations, however, demonstrate that a combination therapy for weight loss with a low caloric diet and exercise is recommended for weight loss due to stronger suppression of insulin resistance and sympathetic activation, which both are known as strong risk factors for cardiovascular events. Although few studies have observed changes in body weight, blood pressure, neurohormonal changes over a long duration such as 2 years, Masuo *et al.* [6] observed more than 30% individuals who initially succeeded to significantly lose weight, had rebound weight gain over 2 years. Understanding mechanisms underlying both type 2 diabetes and obesity may help to achieve weight loss and maintenance of weight loss and the stricter blood glucose goal. Maintenance of weight loss is another key factor to reduce cardiovascular risks in type 2 diabetes in obesity [6].

In addition, most hypertensive patients with diabetes and obesity are very resistant to controlling hypertension and frequently require two or more types of medications to achieve blood pressure goals. Similarly, diabetic patients, especially type 2 diabetic patients with obesity, need higher dose of anti-diabetic medications such as metformin or insulin. However, pharmacological treatments for hypertension and diabetes with weight loss could reduce pharmacological treatment [7, 8].

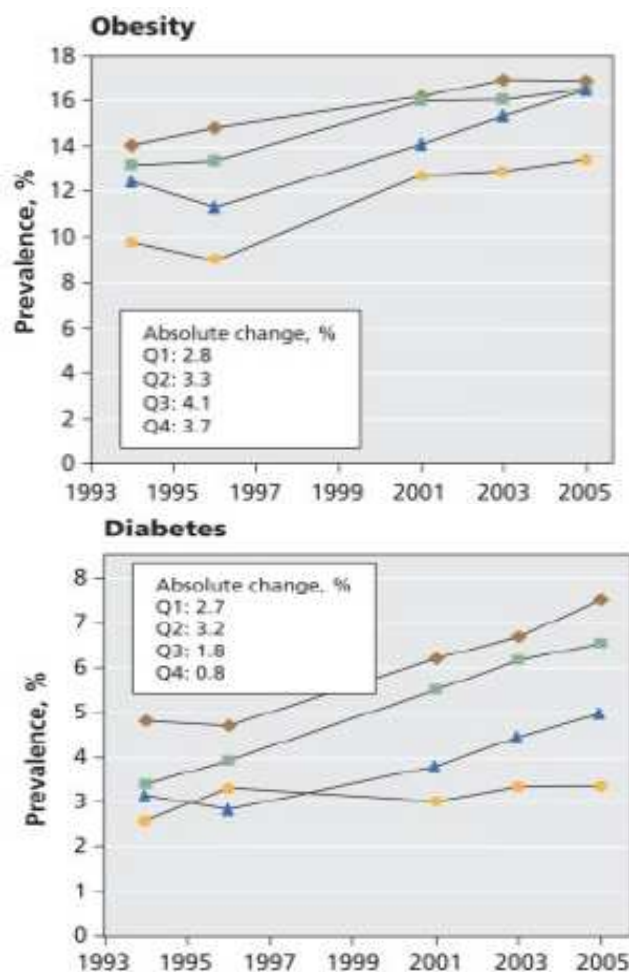


Figure 2. Prevalence of diabetes has increased in parallel with obesity. [Reference 2]

The purpose of this review is to provide, *i)* the importance of lifestyle modifications to delay and prevent type 2 diabetes, *ii)* Lifestyle modification to reduce cardiovascular risks in type 2 diabetes, and *iii)* weight loss for the better pharmacological control on type 2 diabetes and hypertension, which frequently co-exist with type 2 diabetes. *iv)* The mode of weight loss influences different physiological pathways, with calorie restriction and exercise program. *v)* Different mechanisms may contribute to reductions in blood pressure and cardiovascular risks associated with weight loss with the relevant physiological mechanisms at play being dependent on the mode of weight loss.

2. Type 2 diabetes versus Type 1 diabetes

Prevalence of diabetes has increased markedly over the last 20 years in parallel with obesity (Figures 2 and 3) [1, 2]. As of 2010 there are approximately 285 million people with the disease compared to around 30 million in 1985. Long-term complications from high blood sugar can include heart disease, strokes, renal failure, diabetic retinopathy, and diabetic neuropathy.

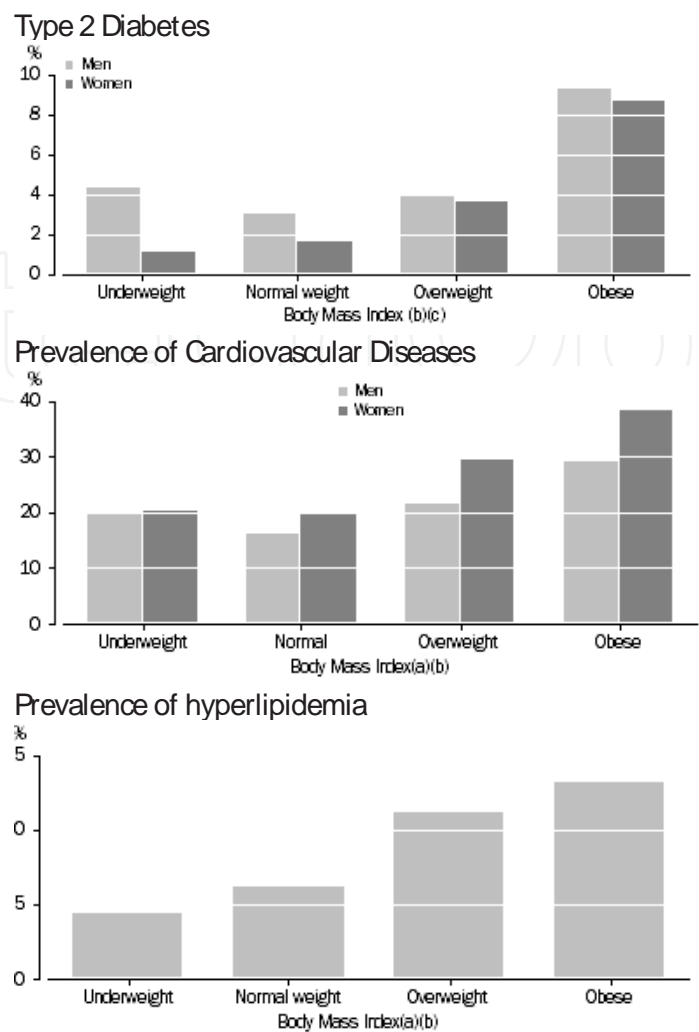


Figure 3. Prevalence of type 2 diabetes, cardiovascular disease and hyperlipidemia (hyper cholesterolemia) increased with obesity in both genders. [Source: National Health Survey, Australia, 2004-2005] Reference [1]

Diabetes mellitus includes type 2 diabetes (formerly noninsulin dependent diabetes), type 1 diabetes (formerly insulin dependent diabetes), and gestational diabetes. These 3 types of diabetes have different characteristics and progress [9]. Ninety percent of diabetic patients are type 2 diabetes and the other 10% are due primarily to diabetes mellitus type 1 and gestational diabetes.

2.1. Diabetes mellitus type 2 (Formerly noninsulin-dependent diabetes mellitus (NIDDM))

Type 2 diabetes is the most common form of diabetes, affecting 90% of all patients with diabetes. This type of diabetes is characterised by metabolic disorder with insulin resistance and relative insulin deficiency [10]. This is in contrast to type 1 diabetes, in which there is an absolute insulin deficiency due to destruction of islet cells in the pancreas [9, 11]. Obesity is thought to be the primary cause of type 2 diabetes in people who are genetically predisposed

to the disease, and obesity has been found to contribute to approximately 55% of case of type 2 diabetes [12].

The disease is strongly genetic in origin but lifestyle factors such as excess weight, inactivity, high blood pressure and poor diet are major risk factors for its development. Symptoms may not show for many years and, by the time they appear, significant problems may have developed. People with type 2 diabetes are twice as likely to suffer cardiovascular disease. The classic symptoms are excess thirst, frequent urination, and constant hunger.

Type 2 diabetes is initially managed by increasing exercise and dietary modification. If blood glucose levels are not adequately lowered by these measures, medications such as metformin or insulin may be needed. In those on insulin, there is typically the requirement to routinely check blood sugar levels.

2.2. Type 1 diabetes (Insulin-dependent diabetes)

Type 1 diabetes is an auto-immune disease targeting on the insulin-producing beta cells in the pancreas. This type of diabetes, also known as juvenile-onset diabetes, accounts for approximately 10% of all people with the disease. In the majority of cases this type of diabetes appears before the patient is 40 years old, triggered by environmental factors such as viruses, diet or chemicals in people genetically predisposed. Patients with type 1 diabetes will require insulin therapy regularly, and should follow a careful diet and exercise plan.

2.3. Gestational diabetes mellitus

Gestational diabetes, or glucose intolerance, is first diagnosed during pregnancy through an oral glucose tolerance test. Between 5.5 and 8.8% of pregnant women develop gestational diabetes in Australia [13], and 2 to 10 percent of all pregnancies in USA [14]. The hormones produced during pregnancy increase the amount of insulin needed to control blood glucose levels. If the body can't meet this increased need for insulin, women can develop gestational diabetes during the late stages of pregnancy.

While the glucose intolerance usually returns to normal after the birth, the mother has a significant risk of developing permanent diabetes while the baby is more likely to develop obesity and impaired glucose tolerance and/or diabetes later in life [15]. Risk factors for gestational diabetes include a family history of diabetes, increasing maternal age, obesity, lack of sleep [16], and being a member of a community or ethnic group with a high risk of developing type 2 diabetes. Self-care and dietary changes are essential in treatment.

3. Prevalence of type 2 diabetes

The prevalence of type 2 diabetes has dramatically increased in parallel in rising prevalence of obesity (Figures 1 and 2), and it increases with obesity (Figure 3). Rates of diabetes in 1985 in worldwide were estimated at 30 million, increasing to 135 million in 1995 and 217 million

	Type 1 Diabetes	Type 2 Diabetes
Diagnosis:	Genetic, environmental and auto-immune factors, idiopathic	Genetic, obesity (central adipose), physical inactivity, high/low birth weight, GDM, poor placental growth, metabolic syndrome
Warning Signs:	Increased thirst & urination, constant hunger, weight loss, blurred vision and extreme tiredness, glycouria	Feeling tired or ill, frequent urination (especially at night), unusual thirst, weight loss, blurred vision, frequent infections and slow wound healing, asymptomatic
Target Groups:	Children/teens	Adults, elderly, ethnic groups
Prone ethnic groups:	All	more common in African American, Latino/Hispanic, indigenous, Asian or Pacific Islander
Bodily Effects:	Believed to be triggered autoimmune destruction of the beta cells; autoimmune attack may occur following a viral infection such as mumps, rubella cytomegalovirus	Appears to be related to aging, sedentary life-style, genetic influence, but mostly obesity
Common physical attributes found:	Mostly Normal or Thin	Mostly Overweight or Obese
You have this when:	Your body makes too little or no insulin.	Your body either cannot produce insulin or does not use it properly.
Estimated percentage of occurrence:	5% -10% of the 171 million of people affected by diabetes in 2000	90% - 95%-of total cases. Although the projected number of Americans that will have type II diabetes in the year 2030 will double from 171 million to 366 million cases
Affected age group:	Between 5 - 25 (maximum numbers in this age group; Type 1 can affect at any age)	Until recently, the only type of diabetes that was common in children was Type 1 diabetes, most children who have Type 2 diabetes have a family history of diabetes, are overweight, and are not very physically active. Usually develops around puberty
Glucose Channels/receptors:	Open and absorb glucose into cell to be utilized by processes after the induction of insulin	Are unable to open and absorb glucose, therefore glucose cannot be utilized by processes; as a result the glucose stays in the blood stream
Cure:	None	Physical exercise, healthy loss of weight & diet control
Treatment:	Insulin Injections, dietary plan, regular check up of blood sugar levels, daily exercise Goals: optimal glucose, prevent/treat chronic complications, enhance health with food/PA, individual nutrition needs	Diet, exercise, weight loss, and in many cases medication. Insulin Injections may also be used, SMBG
Dependency:	Insulin-dependent	Not insulin-dependent
Onset:	Rapid (weeks)	Slow (years)
[Reference, American Diabetes Association-Executive Summary-2012, A-348]		

Table 1. Comparison between type 1 diabetes and type 2 diabetes

in 2005 [17]. This increase is believed to be primarily due to the global population aging, a decrease in exercise, and increasing rates of obesity [18].

The prevalence of diabetes is recognized as a global epidemic by the World Health Organization (WHO) [19]. The World Health Organization (WHO) has reported 346 million people worldwide had diabetes in 2004. Globally as of 2010 it was estimated that there were 285 million people with type 2 diabetes, and this is equivalent to about 6% of the world's adult population [18]. In 2010, diabetic patients were estimated as 316 million people worldwide, and this is equivalent to about 6% of the world's adult population. Importantly, the National Diabetes Fact Sheet 2011 by Centers for Disease Control and Prevention (CDC) pointed out 7.0 million American people (27% of those with diabetes) were not diagnosed and an estimated 79 million Americans have pre-diabetes, indication that much more of the population were affected by diabetes [20, 21]. An estimated 3.4 million people died from consequences of diabetes in 2004, which more than 80% of diabetes deaths occurs in low- and middle-income countries, and diabetes deaths will increase by double between 2005 and 2030 [22]. The five countries with the greatest number of people with diabetes as of 2000 are India, China, the United States, Indonesia, and Japan. Diabetes is common both in the developed and the developing world, but not in the underdeveloped world. Women seem to be at a greater risk as do certain ethnic groups such as South Asians, Pacific Islanders, Latinos, and Native Americans [18]. This may be due to enhanced sensitivity to a Western lifestyle in certain ethnic groups [23].

4. What causes type 2 diabetes?

Many epidemiological studies showed a strong association between obesity and type 2 diabetes, however it is also true that not all obese individuals have type 2 diabetes [20]. Majority of the onset and development of type 2 diabetes is caused by a combination of lifestyle and genetics. Other confounders are also reported to relate to the onset and development of type 2 diabetes: *i.e.* lack of sleep [16], which has been linked to type 2 diabetes through its effect on metabolism [15], nutritional status of a mother during fetal development may also play a role, with one proposed mechanism being that of altered DNA methylation [24]. While some are under personal control, such as diet and obesity, others, such as increasing age, female gender, and genetic susceptibility, is not. The followings are several causes known for type 2 diabetes.

4.1. Lifestyle

A number of lifestyle factors are known to be important to the development of type 2 diabetes, including obesity, lack of physical activity (sedentary life style) [12], poor diet, stress, and urbanization.

Excess body fat is associated with 30% of cases in type 2 diabetes of Chinese and Japanese descent, 60-80% of cases in those of European and African descent, and 100% of Pima Indians and Pacific Islanders [19, 23]. Interestingly, Pima Indians and Pacific Islanders have relatively higher waist-to-hip ratio even if they are not obese, suggesting that abdominal obesity and visceral fat is more important to cause type 2 diabetes.

Dietary factors also influence the risk of developing type 2 diabetes. Consumption of sugar-sweetened drinks in excess is associated with an increased risk. It has been demonstrated saturated fat and trans-fatty acids increase LDL cholesterol, the risk of type 2 diabetes, and cardiovascular risk. Poly-unsaturated, and monounsaturated fat decreasing the risk, but It is recommended to take both in a limited quantity. The American Heart Association has recommended that Americans should limit their intake of saturated fats to 7% of their total calories in a day, while unsaturated fats can form 30% of the calorie intake.

4.2. Genetics

Most cases of diabetes involve many genes, with each being a small contributor to an increased probability of becoming a type 2 diabetic. If one identical twin has diabetes, the chance of the other developing diabetes within his lifetime is greater than 90% while the rate for non-identical siblings is 25-50%. As of 2011, more than 36 genes have been found that contribute to the risk of type 2 diabetes. All of these genes together still only account for 10% of the total heritable component of the disease. The TCF7L2 allele, for example, increases the risk of developing diabetes by 1.5 times and is the greatest risk of the common genetic variants. Most of the genes linked to diabetes are involved in beta cell functions in pancreas.

There are a number of rare cases of diabetes that arise due to an abnormality in a single gene (known as monogenic forms of diabetes or "other specific types of diabetes"). These include maturity onset diabetes of the young (MODY), Donohue syndrome, and Rabson-Mendenhall syndrome, among others. Maturity onset diabetes of the young constitutes 1–5% of all cases of diabetes in young people.

4.3. Medical conditions

There are a number of medications, including glucocorticoids, thiazides, beta blockers, atypical antipsychotics, and statins that can predispose to diabetes [25].

Statins have beneficial effects on reductions of cardiovascular risks through lipids control, and mortality and morbidity in patients with high cardiac risk such as diabetes, coronary heart disease, ischemic heart disease, chronic kidney disease, chronic heart failure, and peripheral vascular disease [26, 27]. National and international clinical guidelines in the management of these cardiovascular disease conditions all advocate for the utilization of statins therapy in appropriate patients. The meta-analysis including 80,771 participants with low cardiac risk showed that all-cause mortality was significantly lower among patients receiving a statin than among controls with a 10-year risk of cardiovascular disease < 20% [28]. Patients in the statin group were also significantly less likely than controls to have nonfatal myocardial infarction, and nonfatal stroke, but the effects did not depend on high- and low-potency statins, or larger reductions in cholesterol. The JUPITER trial [27] and Atherosclerosis Risk in Communities (ARIC) Study [29] demonstrated that suppression of low-grade inflammation by statins improves these clinical outcomes.

Recently, concerns were raised regarding the onset and development of diabetes in statin-treated patients [30]. The meta-analysis studied by Coleman *et al.* [31] showed that statins, as

a class, did not demonstrate a statistically significant positive or negative impact on a patient's risk of developing new-onset type 2 diabetes mellitus, whereas Satter *et al.* [32] observed that statin therapy is associated with a slightly increased risk of development of diabetes using meta-analysis, but the risk is low both in absolute terms and when compared with the reduction in coronary events. Clinical practice in patients with moderate or high cardiovascular risk or existing cardiovascular disease should not change. In 2012, two major studies have addressed the question of whether statins lead to an increase in diabetes, which included the meta-analysis of 33,000 participants enrolled in 5 major clinical trials using statins [33, 34], and analysed data from 153,840 postmenopausal women between 50 and 80 years in the Women Health Initiative Study [30]. The study showed women taking statins had a 48% increased risk of diabetes compared those without statins. The American Heart Association concluded in 2012 that the benefits of statins on lipids-lowering effects and resultant reductions in cardiovascular risks outweighed to the new onset or development of diabetes [35].

Combined bezafibrate/statin therapy is theoretically believed more effective in achieving a comprehensive lipid control and residual cardiovascular risk reduction [36, 37]. The ACCORD Study [38], however, showed that the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke, as compared with simvastatin alone. Based on the beneficial effects of pan-PPAR agonist bezafibrate on glucose metabolism and prevention of new-onset diabetes, one could expect a neutralization of the adverse pro-diabetic effect of statins using the strategy of a combined statin/fibrate therapy [39, 40].

5. Type 2 diabetes mellitus as a risk factor for cardiovascular disease

Several epidemiological studies are available to understand that diabetes is a strong cardiovascular disease risks. A population-based European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study [41], which consisted of 23,455 participants (9,729 men and 15,438 women) followed up from 1994-1998 to 2006, showed that participants with a high risk of the development of diabetes had significantly higher risks of myocardial infarction and stroke than those with a low risk of diabetes development. Subjects at a high risk of diabetes development were also at considerably higher risks of developing cardiovascular complications in general.

The Framingham Heart Study [42] observed that both cardiovascular disease and non-cardiovascular disease mortality rates among individuals with diabetes mellitus were approximately 2-fold higher compared with individuals without diabetes. Non-cardiovascular disease mortality declined among women without diabetes mellitus, while no change in non-cardiovascular disease mortality was observed among women and men with diabetes between the "1950 to 1975" and "1976 to 2001" period. Importantly, individuals with diabetes were at a higher risk of all-cause mortality, especially cardiovascular disease mortality, in both the periods compared to those without diabetes. Another study has shown that diabetes is associated with a substantial increase in all cause and coronary heart disease mortality [43].

Regarding the gender differences in mortality and morbidity of cardiovascular complications, Kanaya *et al.* [44], in their meta-analysis, documented that absolute coronary heart disease death rates were higher in diabetic men compared with diabetic women at every age except the very oldest, however, the excess relative risk of coronary heart disease mortality in women versus men with diabetes was absent after adjusting for classic coronary heart disease risk factors (*i.e.* dyslipidemia, hypertension).

Recently, the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study [45] was performed in 1,123 patients with type 2 diabetes and no symptoms of coronary heart disease using adenosine-stress radionuclide myocardial perfusion imaging from 2000 to 2007. The cumulative cardiac event rate in DIAD was 2.9% over a mean follow-up of 4.8 years for an average of 0.6% per year, which is higher compared to the general population.

The World Health Organization Multinational Study of Vascular Disease in diabetes [46, 47] examined the relationship between excess mortality and proteinuria/hypertension in a stratified random sample of 4,714 diabetic patients aged 35-55 years from 1975 to 1987. Even in the absence of proteinuria and hypertension, standardized mortality rates were significant higher in patients with both type 1 and type 2 diabetes compared to the general population. Standardized mortality was higher in those with type 1 diabetes compared with type 2 diabetes, and the standard mortality rate increased with increasing diabetes duration. In addition, both hypertension and proteinuria had a strikingly high mortality risk by 11-fold for men with type 1 diabetes, and 5 fold for men with type 2 diabetes, indicating that diabetes accompanying cardiovascular disease leads to even higher mortality risk.

Hypertension is twice as frequent in diabetic patients in the general population, and its prevalence is higher in type 2 diabetes than in type 1 diabetes. In type 2 diabetes, the onset of hypertension often precedes the diagnosis of diabetes, whereas in type 1 diabetes it is strictly related to the presence of nephropathy [48].

Further, many studies have shown the strong associations of myocardial infarction [49] and atherosclerosis [50-52]. A number of epidemiological studies provide evidence that diabetes mellitus is a significant risk factor for cardiovascular disease mortality and morbidity [53]. Longer duration of diabetes is a stronger predictor of mortality among diabetic patients. Therefore, people who have diabetes mellitus or strong lifestyle or dietary factors to predict the development of type 2 diabetes [54] should avoid the cardiovascular complications.

6. Neurohormonal characteristics in type 2 diabetes: Insulin resistance and sympathetic activity

It is widely recognized that insulin resistance is a major mechanism of the onset of type 2 diabetes. Insulin resistance in children could predict future glucose intolerance and type 2 diabetes in 10 years [46, 55]. Reduced energy expenditure and resting metabolic rate are predictive of weight gain (obesity). The sympathetic nervous system participates in regulating energy balance through thermogenesis. Many epidemiological and clinical studies have shown

a close relationship between sympathetic nervous system activity and insulin levels in obesity and in weight gain [56, 57]. Elevations of sympathetic nervous system activity and insulin levels during weight gain [58-60] and reductions of sympathetic activity and insulin levels during weight loss [61-64] are typically observed. In addition, The response of the sympathetic nervous system to changes in plasma insulin levels after oral glucose loading (oral glucose tolerance test) are different between subjects with and without insulin resistance [65], between nonobese and obese subjects [66], and between subjects with and without metabolic syndrome [67]. Those observations provide evidence of a strong linkage between the activity of the sympathetic nervous system and insulin levels over glucose metabolisms. Straznicky *et al.* [68] reported that the progress from metabolic syndrome to type 2 diabetes might be associated with increased central sympathetic drive, blunted sympathetic responsiveness, and altered norepinephrine disposition.

Acute hyperglycemia caused sympathetic activation and peripheral vasodilation. Moreover, both acute and chronic hyperglycemia and hyperinsulinemia may enhance adrenergic vasoconstriction and decrease vasodilation in animal models (pithed rats) [69, 70]. Insulin causes forearm vasoconstriction in obese, insulin-resistant hypertensive humans [71]. On the other hand, van Veen *et al.* [72] found that hyperglycemia in the forearm induced vasodilation, but this vasodilation was not modified by hyperinsulinemia.

Huggett *et al.* [66] examined muscle sympathetic nerve activity (MSNA) in four groups of subjects, patients with essential hypertension and type 2 diabetes, patients with type 2 diabetes alone, patients with essential hypertension alone, and healthy normotensive controls. They found higher MSNA in hypertensive-type 2 diabetic patients compared with hypertensive alone patients or type 2 diabetic alone patients, and higher MSNA in hypertensive alone patients or type 2 diabetic alone patients compared with healthy normotensive controls. Fasting insulin levels were greater in hypertensive-type 2 diabetic patients and type 2 diabetic patients compared to hypertensive patients or healthy normotensive subjects. These findings provided evidence that type 2 diabetic patients had elevated sympathetic nerve activity regardless of the prevailing blood pressure levels, and that the combination of hypertension and type 2 diabetes resulted in an augmentation in sympathetic nerve activity and levels of plasma insulin.

Moreover, stimulation of the renin-angiotensin-aldosterone system (RAAS) is frequently demonstrated in type 2 diabetes [73], and may be related to insulin resistance either via direct or indirect mechanisms [74].

7. Treatments for type 2 diabetes

Weight loss is recommended as the first line of treatment for type 2 diabetes and hypertension associated with obesity, because obesity is the primary cause for insulin resistance, metabolic syndrome and type 2 diabetes. Indeed, lifestyle modification including a low caloric diet, reducing sedentary behaviour and exercise form the foundation of all therapy. For the subjects

who are more severely obese or unable to undertake an exercise program, bariatric surgery is recommended.

7.1. Lifestyle modification for weight loss

Weight loss is recommended as the first-line treatment for obesity-related type 2 diabetes and hypertension. The objective of treatment for obesity, type 2 diabetes and hypertension is both to reduce the high risk of cardiovascular events and to prevent or delay the onset of type 2 diabetes and complications. Lifestyle intervention with diet and exercise leading to weight loss prevents and delays the onset of type 2 diabetes or glucose intolerance [75]. Weight loss may also prevent cardiovascular- and renal-complications [76-79], and renal function and left ventricular hypertrophy as a marker for future cardiac events in obese individuals with metabolic syndrome and hypertension [77, 80]. The US Diabetes Prevention Program [81] and the Oslo Diet and Exercise Study [82] have shown marked clinical benefits with lifestyle intervention, and modest weight loss, on the resolution of the metabolic syndrome and type 2 diabetes. A limited number of epidemiological studies have shown that intentional weight loss may be associated with increased mortality and fat loss may reduce the all-cause mortality rate [83].

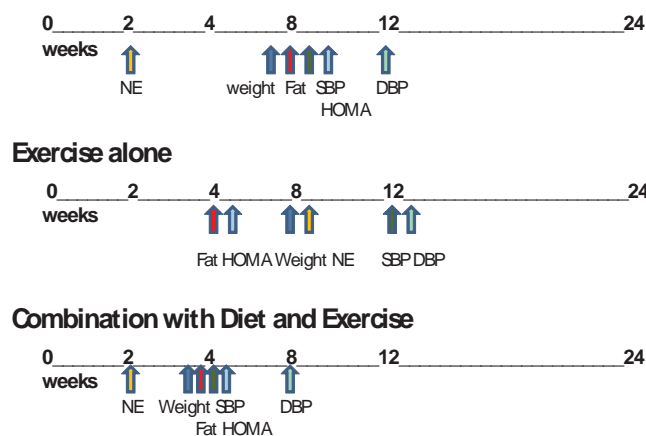
Cohort studies with lifestyle intervention [84] and case control studies with bariatric surgeries [85, 86] also provide some evidence that intentional weight loss has long-term benefits on all cause mortality in overweight adults. In a cohort of patients enrolled in a cardiac rehabilitation program, weight loss was associated with favourable long-term outcomes on the composite end-point of mortality and acute cardiovascular events (fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, emergent revascularization for unstable angina pectoris, and congestive heart failure) [87].

Many clinical studies have demonstrated that weight loss associated with life-style modification adds to the first line treatment for diabetes mellitus and the efficacy of antihypertensive pharmacological treatments [8], however, maintaining weight loss is often the greatest challenge [5, 6, 88].

7.1.1. Calorie restricted diet versus aerobic exercise

The American Diabetes Association (ADA) has recommended for the maintenance of a healthy weight to prevent and control diabetes as following; (i) more than 2.5 hours of exercise per week, (ii) having a modest fat intake (approximately 30% of energy supply), and (iii) rating sufficient fiber [89]. Recently, several investigations [4, 5, 90] compared the effects on weight loss between calorie restriction (diet) and exercise. They showed that combined intervention with diet and exercise proved to be effective in weight reduction than diet alone or exercise alone. Masuo *et al.* [5] reported that the group with mild exercise alone had greater and faster loss of total body fat-mass compared to the diet alone group, whereas Toji *et al.* [90] reported that exercise intervention alone was not found to be effective on weight loss. There are discordant results on the effects of diet and exercise on weight loss and weight loss-induced blood pressure reductions, however many large cohort interventions and clinical studies have

Figure 4: When significant changes were observed
 comparisons between a calorie restricted diet vs. mild exercise alone vs.
 combination with diet + exercise over 24 weeks



Reference [5]

NE, plasma norepinephrine as index of sympathetic activity;
 HOMA, HOMA-IR (homeostasis model assessment of insulin resistance) as an index of insulin resistance; Weight, body weight; Fat, total body fat-mass; SBP, systolic blood pressure;
 DBP, diastolic blood pressure.

Figure 4. When significant changes were observed comparisons between a calorie restricted diet vs. mild exercise alone vs. combination with diet + exercise over 24 weeks

shown combination weight loss regimens with mild calorie restriction and mild exercise was the most effective for significant weight loss compared to diet alone or exercise alone.

A low caloric diet and exercise exert different effects on insulin resistance, the RAAS, and sympathetic nervous activity in obese hypertensive subjects, even though similar weight loss was observed [4, 5]. Low caloric diet may be prominent for normalization of sympathetic nervous activity and exercise may be related more to normalization of insulin resistance [5, 88] (Figure 4). They previously observed that baseline plasma norepinephrine levels could predict future weight gain and weight gain-induced blood pressure elevation over 5 years in a longitudinal study [91], resistant weight loss by weight loss intervention with combination of calorie restriction and exercise intervention over 2 years. [6, 88] Similarly, Straznicky *et al.* [92] showed baseline sympathetic tone measured by muscle sympathetic nervous activity and nutritional responsiveness could predict the success of dietary weight loss, but not exercise, supporting the results including that the sympathetic nervous activity plays major mechanisms and roles on diet-induced weight loss pointed by Masuo, *et al.* [5]. Ribeiro *et al.* [93], Trombetta *et al.* [94] and Tonacio *et al.* [95] compared the effects of a low caloric diet and exercise on blood pressure lowering and forearm blood flow. They observed that only exercise, not diet, significantly increased forearm blood flow.

Santarpia *et al.* [96] reviewed the effectiveness of weight loss regimens and body composition after weight loss between diet and exercise. At a long term follow up (over one year),

relatively high protein, moderately low calorie, low glycemic index diets, associated with a daily, moderate intensity, physical exercise (of at least 30 min), appear to be more successful in limiting long term rebound, maintaining fat-free-mass and achieving the highest fat loss. Diet alone or physical exercise alone does not produce similar results. Adequate dietetic advice plus regular physical exercise avoid the fat-free-mass loss usually observed in the rebound of the weight cycling syndrome and prevent the onset of sarcopenic obesity.

Exercise training is important for weight loss and to prevent rebound weight gain after significant weight loss. Public health interventions promoting walking are likely to be the most successful. Indeed, walking is unique because of its safety, accessibility, and popularity. It is noteworthy that there is a clear dissociation between the adaptation of cardiopulmonary fitness and the improvements in the metabolic risk profile such as insulin resistance and sympathetic activation, which can be induced by endurance training programs. Dumortier *et al.* [97] also reported that individualized low intensity endurance aerobic training improves lipid oxidation, body composition and insulin resistance. It appears that as long as the increase in energy expenditure is sufficient, low-intensity endurance exercise is likely to generate beneficial metabolic effects that would be essentially similar to those produced by high-intensity exercise [98]. The clinician should therefore focus on the improvement of the metabolic profile rather than on weight loss alone [98].

7.1.2. Dietary

7.1.2.1. Saturated fat versus unsaturated fat

Recently, several large cohort studies have shown that saturated fat, which comes mainly from animal sources of food, raises LDL cholesterol and links strongly to cardiovascular risk [99, 100]. Saturated fats are needed for the production of hormones, the stabilization of cellular membranes, the padding around organs, and for energy. A deficiency in the consumption of saturated fats can lead to age-related declines in white blood cell function, along with dysfunction of the immune system and cancer [101]; however, a high content of saturated fat can lead to coronary heart disease [102], ischemic heart disease, and atherosclerosis and increase the chances of stroke.

Consistent evidence from prospective observational studies of habitual trans fatty acids (TFA) consumption and retrospective observational studies using TFA biomarkers indicates that TFA consumption increases risk of clinical coronary heart disease, and other disease outcomes such as cancer [102].

Unsaturated fats are known to increase the levels of High Density Lipoprotein (HDL cholesterol) and hence decrease LDL and VLDL cholesterol. Both types of unsaturated fat- mono-unsaturated and poly-unsaturated fats can replace saturated fats in the diet. Substituting saturated fats with unsaturated fats help to lower levels of total cholesterol and LDL cholesterol in the blood. However, intake of unsaturated fats in very high amounts can also increase the risk of coronary heart diseases.

- i. **Monounsaturated fat:** This is a type of fat found in a variety of foods and oils. Studies show that eating foods rich in monounsaturated fats (MUFAs) improves blood

cholesterol levels, which can decrease the risk of heart disease. Research also shows that MUFAs may benefit insulin levels and blood sugar control, which can be especially helpful for type 2 diabetes.

- ii. **Polyunsaturated fat (PUFAs):** This is a type of fat found mostly in plant-based foods and oils. The Swedish Mammography Cohort study including 34, 670 women with a mean follow-up of 10.4 years, showed that intake of long-chain omega-3 PUFAs is inversely associated with risk of stroke, whereas dietary cholesterol is positively associated with risk [103]. Similarly, Chowdhury *et al.* [104] observed in meta-analysis that moderate, inverse associations of fish consumption and long chain omega 3 fatty acids with cerebrovascular risk, but long chain omega 3 fatty acids measured as circulating biomarkers in observational studies or supplements in primary and secondary prevention trials were not associated with cerebrovascular disease. The beneficial effect of fish intake on cerebrovascular risk is likely to be mediated through the interplay of a wide range of nutrients abundant in fish. PUFAs decrease the risk of type 2 diabetes. One type of polyunsaturated fat, a long chain omega-3 fatty acids is especially beneficial to coronary heart disease.
- iii. **Trans-fatty acids (TFA):** Growing evidence indicates that trans-fatty acids (TFA) adversely affect cardiovascular health. Controlled trials and observational studies provide concordant evidence that consumption of TFA from partially hydrogenated oils adversely affects multiple cardiovascular risk factors, and contributes significantly to increased risk of coronary heart disease events. The public health implications of ruminant TFA consumption appear much more limited. Nurses' health study showed that *trans*-fat intake was associated with increased risk of coronary heart disease, particularly for younger women [105]. Interestingly, incidence of insulin resistance is lowered with diets higher in monounsaturated fats (especially oleic acid), while the opposite is true for diets high in polyunsaturated fats (especially large amounts of arachidonic acid) as well as saturated fats. This relationship between dietary fats and insulin resistance is presumed secondary to the relationship between insulin resistance and inflammation, which is partially modulated by dietary fat ratios (Omega3/6/9) with both omega 3 and 9 thought to be anti-inflammatory, and omega 6 pro-inflammatory [106].

It is recommended to take both in a limited quantity. The American Heart Association has recommended that Americans should limit their intake of saturated fats to 7% of their total calories in a day, while unsaturated fats can form 30% of the calorie intake to reduced cardiovascular risks.

7.1.2.2. *Special diet*

i. **Low Carbohydrate Diet**

Low-carbohydrate diets are dietary programs that restrict carbohydrate consumption usually for weight control or for the treatment of obesity. The term "low-carbohydrate diet" is generally applied to diets that restrict carbohydrates to less than 20% of caloric intake, but can also refer

to diets that simply restrict or limit carbohydrates. Recently, the low carbohydrate diets has been spotlighted due to strong effects on weight loss, but many investigations have also shown no benefits on the reductions on cardiovascular risk as the major aim of weight loss.

A study of more than 100,000 people over more than 20 years within “the Nurses' Health Study” observationally concluded that a low-carbohydrate diet high in vegetables, with a large proportion of proteins and oils coming from plant sources, decreases mortality with a hazard ratio of 0.8. In contrast, a low-carbohydrate diet with largely animal sources of protein and fat increases mortality, with a hazard ratio of 1.1, although there were criticisms on the methods [107]. A 2003 meta-analysis that included randomized controlled trials found that “low-carbohydrate, non-energy-restricted diets, appear to be at least as effective as low-fat, energy-restricted diets in inducing weight loss for up to 1 year [108]. Gardner *et al.* [109] compared the 4 special diet including the Atkins (a low-carbohydrate), Zone (by Barry Sears PhD, 40% carbohydrates, 30% protein, and 30% fats), Ornish (very low fat diet), and LEARN diets (55% to 60% energy from carbohydrate and less than 10% energy from saturated fat) to evaluate the effects of weight loss, metabolic effects and the risk over 1 year in 311 obese, non-diabetic, premenopausal women with randomized design. Weight loss was significantly greater for women in the Atkins diet group (low carbohydrate) compared with the other 3 diet groups at 12 months, and weight loss in the other 3 groups were similar, but at 12 months, secondary outcomes for the Atkins group were more favorable metabolic effects than the other diet groups. While questions remain about long-term effects and mechanisms, a low-carbohydrate, high-protein, high-fat diet may be considered a feasible alternative recommendation for weight loss. However, some investigators suggested that that one of the reasons people lose weight on low carbohydrate diet is related to the phenomenon of spontaneous reduction in food intake [110].

Previously, in routine practice a reduced-carbohydrate, higher protein diet was recommended approach to reducing the risk of cardiovascular disease and type 2 diabetes [111]. In 2004, the American Diabetes Association (ADA) affirmed its acceptance of carbohydrate-controlled diets as an effective treatment for short-term (up to one year) weight loss among obese people suffering from type 2 diabetes [112]. And the American Diabetes Association (ADA) revised their “*Nutrition Recommendations and Interventions for Diabetes in 2008*” to acknowledge low-carbohydrate diets as a legitimate weight-loss plan [113]. The recommendation, however, fell short of endorsing low-carbohydrate diets as a long-term health plan nor do they give any preference to these diets. On the other hand, the official statement from the American Heart Association (AHA) regarding these diets states categorically that the association doesn't recommend high-protein diets [35]. A science advisory from the AHA further states the association's belief that these diets are associated with increased risk for coronary heart disease [114, 115]. The AHA has been one of the most adamant opponents of low-carbohydrate diets. The American Heart Association supported low-fat and low-saturated-fat diets, but that a low-carbohydrate diet could not potentially meet AHA guidelines.

ii. Low fat diet

Recently, the effectiveness of low-fat high- protein and low-fat high-carbohydrate dietary advice on weight loss were compared using group-based interventions, among overweight

people with type 2 diabetes. However, in a 'real-world' setting, prescription of an energy-reduced low-fat diet, with either increased protein or carbohydrate, results in similar modest losses in weight, waist circumference and metabolic benefits over 2 years [116].

Ebbeling *et al.* [117] investigated the effect of dietary composition on energy expenditure during weight-loss maintenance among the 3 different diet groups (low-fat diet, low-glycemic index diet, and very low carbohydrate diet) with a controlled 3-way crossover design involving 21 overweight and obese young adults each for 4 weeks. Resting energy expenditure (REE), total energy expenditure (TEE), hormone levels, and metabolic syndrome components at pre-weight-loss were compared. Decreases in REE and TEE following 10% or 15% weight loss were greatest with the low-fat diet, intermediate with the low-glycemic index diet, and least with the very low-carbohydrate diet, but metabolic or hormonal parameters were similar between 3 groups.

iii. Low glycemic index

The concept of the glycemic index was developed about 1981 by Dr. David Jenkins to account for variances in speed of digestion of carbohydrates. This concept classifies foods according to the rapidity of their effect on blood sugar levels – with fast digesting simple carbohydrates causing a sharper increase and slower digesting complex carbohydrates such as whole grains a slower one. The concept has been extended to include amount of carbohydrate actually absorbed as well, despite differences in glycemic index [118].

7.2. Pharmacological treatments for type 2 diabetes

If the individuals failed to improve glucose levels or HbA1c, pharmacological therapy is required. The first-line oral agents should minimize the degree of insulin resistance and suppress hepatic glucose production rather than increase plasma insulin concentrations. The decision to include thiazolidinediones (TZDs) and metformin as first-line therapy draws from the algorithm proposed by Wyne *et al.* [118]. Garber *et al.* [120] reported that Initial combination treatment with glyburide/metformin tablets produces greater improvements in glycemic control than either glyburide or metformin monotherapy.

The goal for glucose control is shown in Table 2 [11, 121]. Stimulating insulin secretion and minimizing insulin resistance both have the potential to bring a patient to goal, but it is theorized that bringing a patient to goal by reducing insulin resistance is more likely to reduce the macro-vascular complications and cardiovascular risks.

Based on several long-term, prospective studies which showed the significant reductions in cardiovascular risks associated with diabetes, the American Diabetes Association and American Association of Clinical Endocrinologists set forth standards and guidelines for the medical management of diabetes [11]. The recommendations clearly outline a multifactorial plan for managing diabetes and reducing complications [11], but they do not provide specific recommendations for selection and titration of pharmacological treatment. Pharmacological treatment for glucose control aims to reduce cardiovascular risk and to delay diabetic complications.

Glycemic control	A1C goal of < 7.0%	Measure every 3 months
Blood pressure control	< 130/80 mmHg	Every visit
Lipid control LDL	< 70 mg/dl†	Measure yearly or
Triglycerides	< 150 mg/dl	more frequently
HDL	> 45 mg/dl if	goals are not met
Urine protein Microalbuminuria	<30 mg/24 hours	Measure yearly

*American Diabetes Association Standards of medical care for patients with diabetes mellitus. *Diabetes Care* 26 (Suppl.):S33–S50, 2003.

†National Cholesterol Education Program: Implications of clinical trials for the ATP

Table 2. Diabetes Control Goals (by American Diabetes Association) Goals Endpoints Assessment

Pharmacological treatment for the management of obesity is primarily aimed at weight loss, weight loss maintenance and cardiovascular risk reduction. Anti-obesity agents decrease appetite, reduce absorption of fat or increase energy expenditure. Recently, anti-obesity drugs such as orlistat, sibtramine and rimonabant have been developed and placed on markets, however, the latter two were withdrawn from markets in the United States, Europe and Australia due to serious adverse events including psychiatric and cardiovascular related concerns. Recently, contrave, a combination of two approved drugs of bupropion and naltrexone, completed Phase III trials with significant weight loss and was approved by FDA in 2010, but subsequently the FDA declined to approve contrave due to serious cardiovascular adverse events in 2011 [122]. A contrave cardiovascular outcome trial, called “Light Study”, is ongoing and is expected to be completed by the first quarter of 2013. Importantly, obesity is, at least, in part, determined by genetic backgrounds [123], suggesting that a genetic approach to limiting obesity may find a place in the future.

7.3. Bariatric surgery

Gastric bypass and adjustable gastric banding are the two most commonly performed bariatric procedures for the treatment of morbid obesity or obesity which is resistant to lifestyle modification such as a low caloric diet plus exercise. Multiple mechanisms contribute to the improved glucose metabolism seen after bariatric surgery, including caloric restriction, changes in the enteroinsular axis, alterations in the adipoinsular axis, release of nutrient-stimulated hormones from endocrine organs, stimulation from the nervous system, and psychosocial aspects including a dramatic improvement in quality of life [124]. Dixon *et al.* [86, 125] showed that gastric banding induced significant weight loss and resulted in better glucose control and less need for diabetes medication than conventional approaches to weight loss and diabetes control in a randomized controlled study in obese subjects with recently diagnosed type 2 diabetes. Koshy *et al.* [124] and other investigators [126, 127] compared the effects on weight loss, mortality, morbidity and changes in quality of life in subjects with either gastric bypass or gastric banding. The percent of excess weight loss at 4 years was higher in the gastric

bypass group compared to the gastric banding group. Postoperative HOMA-IR correlated with % weight loss [126]. Concurrent with restoration of insulin sensitivity and decreases in plasma leptin were dramatic decreases in skeletal muscle at 3 and 9 months after gastric banding and a significant decrease in peroxisome proliferation activated receptor- α -regulated genes at 9 months. Gumbs *et al.* [128] speculated that a decrease in fat mass after bariatric surgery significantly affected circulating adipocytokines, which favourably influenced insulin resistance. Improvements in glucose metabolism and insulin resistance following bariatric surgery occur, in the short-term from decreased stimulation of the entero-insular axis by restricted calorie intake and in the long-term by decreased release of adipocytokines due to reduced fat mass. Leptin levels drop and adiponectin levels rise following laparoscopic adjustable gastric banding and gastric bypass. These changes correlate with weight loss and improvement in insulin sensitivity [128].

All forms of weight loss surgery lead to calorie restriction, weight loss, decrease in fat mass, and improvement in insulin resistance, type 2 diabetes mellitus, obesity and obesity-related hypertension [127]. Left ventricular relaxation impairment, assessed by tissue Doppler imaging, normalized 9 months after surgery [129]. Laparoscopic gastric bypass and gastric banding are both safe and effective approaches for the treatment of morbid obesity, but gastric bypass surgery seems to exert a better early weight loss and more rapid ameliorative effects on insulin resistance and adipocytokines, muscle metabolism and left ventricular function.

8. Conclusion

The prevalence of diabetes, especially type 2 diabetes and hypertension are significantly increased due, at least in part, to the increased prevalence of obesity. Type 2 diabetes is frequently associated with obesity, and is an important risk factor for cardiovascular morbidity and mortality and cardiac- and renal complications. Type 2 diabetes, hypertension and obesity are characterized by stimulation of the renin-angiotensin-aldosterone system (RAAS), elevated sympathetic activity and insulin resistance. Importantly, these characteristics, themselves, confer cardiovascular risk. Therefore, treatments for type 2 diabetes should be selected from favourable effects on stimulated RAAS, elevated sympathetic nervous system activity, insulin and leptin resistance.

Weight loss is recommended as the first line of treatment for type 2 diabetes and hypertension associated with type 2 diabetes in obesity. Lifestyle modification such as a caloric restricted diet, reducing sedentary behaviour and increases in exercise form the basis of all therapy. Weight loss treated with lifestyle modification including calorie restriction and/or exercise causes normalization of stimulated RAAS, sympathetic activation, insulin resistance, and hyperleptinemia. Recently, Masuo *et al.* [5] and Straznicky *et al.* [4] have shown that low caloric diet and exercise have different effects on insulin resistance, the RAAS, and sympathetic nervous activity in obese hypertensive subjects, even though similar weight loss was observed. Exercise had stronger effects on normalizing the RAAS

stimulation, sympathetic activation and insulin resistance compared to diet only. The observations demonstrate that a combination therapy for weight loss with a low caloric diet and exercise is recommended for weight loss due to stronger suppression of insulin resistance and sympathetic activation, which both, themselves, are known as risk factors for cardiovascular events. Although few studies have observed changes in body weight, blood pressure, RAAS, sympathetic nervous activity, insulin resistance and leptin resistance over a long duration such as more than 2 years, Masuo *et al.* [6] observed more than 30% individuals who initially succeeded to significantly lose weight, had rebound weight gain over 2 years. Maintenance of weight loss is another key factor to delay and prevent type 2 diabetes and to reduce cardiovascular risks in type 2 diabetes in obesity.

In addition, special diets such as a low carbohydrate diet were reported as beneficial on weight loss previously, but it might cause an increase in cardiac risk. The official statement from American Heart Association reported that high-protein diet and low carbohydrate diet are not recommended diets due to increases in cardiovascular risk.

Gastric bypass and adjustable gastric banding are the two most commonly performed bariatric procedures for the treatment of morbid obesity or obesity which is resistant to lifestyle modification such as a low caloric diet plus exercise. Weight loss by bariatric surgery leads to improvement or normalization of glucose metabolisms from multiple mechanisms including caloric restriction, changes in the enteroinsular axis, alterations in the adipoinsular axis, release of nutrient-stimulated hormones from endocrine organs, stimulation from the nervous system, and psychosocial aspects including a dramatic improvement in quality of life.

Understanding the mechanisms underlying type 2 diabetes in obesity may help to achieve weight loss and maintenance of weight loss and resultant better control on type 2 diabetes, and delay and prevent the onset of type 2 diabetes or reduce complications.

This review provides information regarding, *i*) the importance of lifestyle medication on type 2 diabetes in obesity, *ii*) different effects of lifestyle modifications on weight loss and neuro-hormonal parameters between diet and exercise, and *iii*) the mode of weight loss and how it influences different physiological pathways. Different mechanisms may contribute to control in blood glucose levels and blood pressure and cardiovascular risks associated with weight loss with the relevant physiological mechanisms at play being dependent on the mode of weight loss.

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