Body composition in the pathogenesis and management of diabetes: a Malaysian perspective

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There is an increasing prevalence of diabetes mellitus around the world associated with rapid socio-cultural development and changing lifestyles. Increased prevalence of obesity, with a higher consumption of animal products and lower consumption of fruits and vegetables, increases the risk of diabetes mellitus and other chronic degenerative diseases. Insulin-dependent diabetes (IDD) is caused by insulin deficiency, whereas the main feature of non-insulin-dependent diabetes (NIDD) which accounts for more than 90% of diabetics, is hyperinsulinemia and insulin resistance, which may eventually lead to actual insulin deficiency. Hyperinsulinemia is undesirable because it increases the risk of developing vascular disease. In Malaysia, the prevalence of NIDD in some communities now exceeds 5%, and of impaired glucose tolerance 10%. Along with these increases in prevalence of hyperglycemia are increases in prevalence of overweight (BMI>25) and almost certainly abdominal fatness. In terms of management, nutrition is given priority. Insulin and hypoglycemic drugs (sulphonylureas or biguanides), where required, may adversely affect body composition if overused. Newer therapeutic strategies require greater attention to the underlying problem in NIDD of abdominal fatness by attention to the relevant nutritional factors, physical activity and other lifestyle factors like cigarette smoking and alcohol. The greater impact of obesity and diabetes on Malaysian women as opposed to men also needs to be addressed.

Introduction

Diabetes mellitus was described as early as 1600 BC as a disease with polyuria and insatiable thirst but the detailed description of the disease and its pathogenesis did not exist until the nineteenth century. This disease occurs in almost all populations; however, the prevalence varies depending on the population, its age structure, genetic background and lifestyle. High prevalences are found among the Pima Indians in North America, Nauruans, Indians and Australian Aborigines[1] and low prevalence among the Melanesians in Solomon Islands. Part of the heterogenity between populations is probably accounted for by body composition, in turn dependent on diet, physical activity and substance abuse, over and above genetic background[2]. The present report draws on recent observations of increasing prevalences among Malaysians.

Genetic vs environmental factors

Community-based studies from Malaysia show that the prevalence of diabetes is highest among urban Malays and is lower where the socio-economic development is less (Table 1). However, urban Malays have lower prevalences of impaired glucose tolerance (IGT) compared to their rural counterparts. On the other hand, the prevalence of diabetes mellitus and IGT among Malaysian aborigines (Orang Asli) is very low in all locations. Certain genetic factors for the moment probably protect the Orang Asli from the disease, whereas environmental influences have already increased the prevalence among genetically susceptible Malays. Community comparisons of fasting, 2 hour post-glucose load and Hb A1 values support an environmental influence on diabetes occurrence (Table 2).

Nutrition and diabetes mellitus

Various epidemiological studies have shown that a high consumption of refined carbohydrates and fats, low intake of dietary fibre, together with obesity and on inactive lifestyle contribute to the development of non-insulin-dependent diabetes (NIDD)[4-6]. Increased per capita energy consumption per day, especially of oils and fats, animal products and sugar, with a concomitant decline in the dietary energy from complex carbohydrates such as cereals and other plant products (pulses, nuts and oilseeds, fruits and vegetables) are associated with a high risk of developing NIDD. Ingestion of carbohydrates has not been shown to increase the risk of diabetes except by virtue of contributing to excessive weight gain[7], although there is interest in partial substitution of carbohydrate with monounsaturated oils, as in the Mediterranean diet, as a way of minimizing hyperglycemia[19a].

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Table 1. Crude and adjusted prevalence rates of diabetes mellitus and IGT (per cent)[3].

Stages of development	Diabetes mellitus			IGT		
	crude rate	age-adjusted*	95% It†	crude rate	age-adjusted	95% CI
Remote rural						
Lanai (n=110) (ABO)	0.0	0.0	–	3.3	4.9	0.6–17.6
Ulu Sungai (n=136) (MAL)	2.8	2.7	0.6–8.1	14.8	15.0	8.6–24.0
Rural						
Betau (n=136) (ABO)	1.3	1.7	0.1–9.5	10.7	12.6	5.5–25.2
Koyan (n=132) (MAL)	6.7	7.4	3.0–15.5	10.5	8.5	4.3–15.3
Urban						
Lanjan (n=75) (ABO)	0.0	0.0	–	0.0	0.0	–
Kg. Kerinci (n=92)	8.2	7.7	2.9–16.9	9.6	7.6	3.0–16.0

ABO = Orang Asli. MAL = Malays.
* Five-year age-specific rates (30–64 years) were calculated and standardization was performed using the direct method against the standard population of Segi.
† 95% confidence interval based on Poisson distribution.

Table 2. Blood glucose and HbA1 by social development[3].

Stages of development	Fasting blood glucose (mM)	2 hours post glucose load (mM)	HbA1 (%)
Remote rural			
Lanai Aborigines settlement			
n	111	98	87
means±sd	5.0±1.0*	5.1±1.7*	4.5±0.8*
Ulu Sungai Malay village			
n	152	142	100
means±sd	5.4±1.7	6.1±3.2	5.5±1.7
Rural			
Betau Aborigines settlement			
n	136	115	74
means±sd	4.8±0.5†	5.3±1.3†	4.4±0.5†
Sungai Koyan Malays resettlement scheme			
n	114	109	78
means±sd	5.1±0.8	6.3±2.5	5.6±1.7
Urban			
Lanjan Aborigines village			
n	73	70	73
means±sd	5.1±0.8	5.0±1.2§	4.8±0.6§
Kerinci Malays village			
n	90	81	89
means±sd	5.3±1.9	6.1±3.8	5.8±1.8

Values are means±sd.
*$P<0.05$ vs remote rural Malays.
†$P<0.05$ vs rural Malays.
§$P<0.05$ vs urban Malays.

Epidemiology of obesity and diabetes mellitus

Overweight and obesity are important determinants of NIDD whether in the city or in the village. Data available from epidemiologic studies and surveys in the USA indicates that 24% of American women and 22% of men are obese, by criteria of relative body weight (>120%) or BMI >27.5 kg.m^{-2}. In general, obesity is common among women from lower socio-economic groups[8] and with lower education. The prevalence of overweight and obesity (BMI ≥25) in developing countries such as Malaysia is on an upward trend (Table 3), for urban subjects about 25–30% and rural subjects 5-15%. The prevalence of diabetes among overweight Malaysian subjects BMI ≥25 was 7.3% (9/123) compared to 1.6% (9/560) with BMI <25[3]. Malay females have a six-fold risk of developing diabetes compared to males, and they also have a greater prevalence of overweight and obesity.

Pathogenesis of diabetes mellitus

There is a complex interaction between genetic predisposition and environmental factors in the pathogenesis of diabetes. Diabetes is not a single disorder but a heterogenous syndrome with varying pathogeneses. There are broadly two different forms of the disease type I (insulin-dependent, IDD) and type II (non-insulin-dependent, NIDD)[9]. Approximately 90% of diabetics are type II. The differences in characteristics are shown in Table 4. The development of type I (IDD) diabetes is based on a chronic, progressive inflammation of the islet cells (insulinitis) due to the presence of antibodies against the cells. Hyperglycemia develops because of insulin deficiency of the B-cells. Environmental factors, possibly including diet are increasingly regarded as important in the pathogenesis. Type II diabetes (NIDD) is related to insulin resistance and defective or insufficient insulin receptors.

Body composition and NIDD

The prevalence of overweight among people with NIDD is more than 80%; that of abdominal obesity may even be higher. Individuals who are 40% overweight have almost a seven times greater chance of having diabetes mellitus as individuals of normal weight (Figure 1). Diabetic morbidity also rises as body weight increases[7]. The predominant and most characteristic anatomic changes among obese individuals is the excessive accumulation of adipose tissue or increased body fat content in certain parts of the body. Determination of overfatness by skin fold thickness (SFT) and by BMI for total body fatness have become the most widely used means of assessing body fatness[10]. With SFT and truncal circumferences, distribution in body fatness can also be ascertained.

Many studies have shown that obesity as indicated by body mass index (BMI) is significantly associated with incidence or prevalence of diabetes[11-13]. Other nutritional indices such as mid-arm circumference (MAC) and

Table 3. Prevalence of overweight among Malaysians as indicated by BMI[4].

Age groups (years)	Population	Number	Gender	Criteria of overweight (BMI) (kg, m^{-2})	Prevalence of overweight
18+	rural Malays	522	male	≥25.0	5%
18+	rural Malays	965	female	≥25.0	15%
25–34	Urban executives	146	male	25–30	26%
35–44	of mixed	209			29%
45–54	ethnicity	51			33%

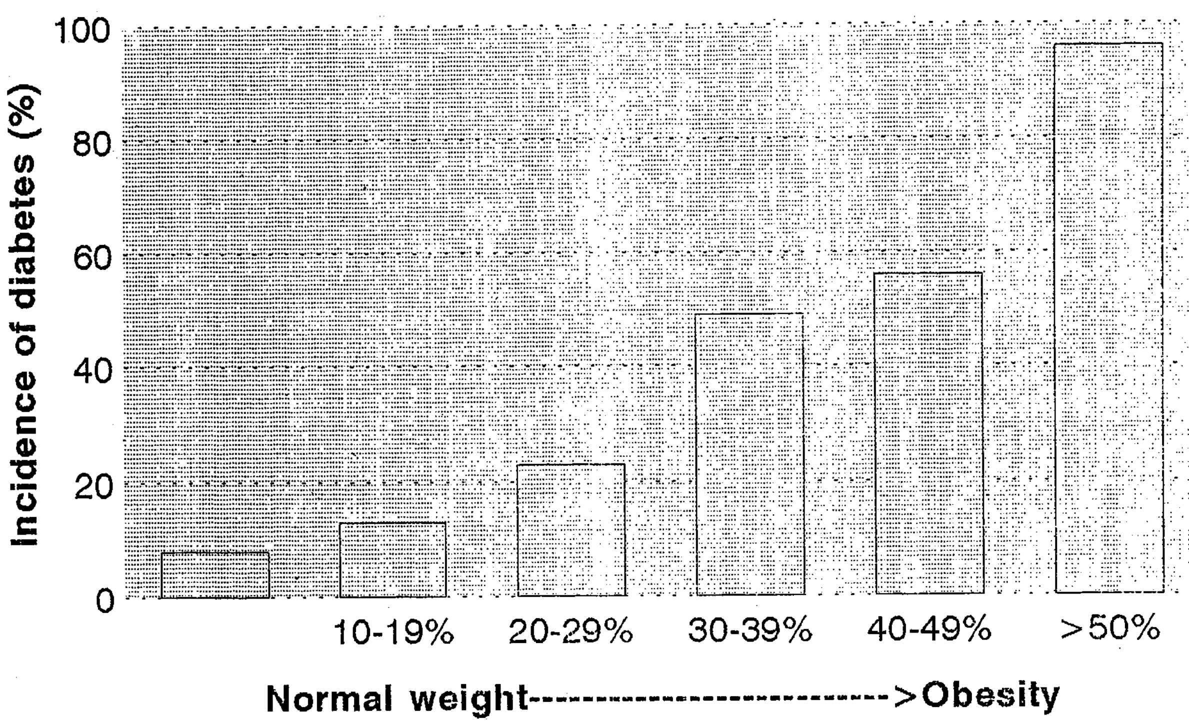

Fig. Incidence of diabetes and body weight (from Diabetes Source Book, 1969).

Table 4. Comparison between IDD and NIDD.

IDDM (type I)	NIDDM (type II)
Prevalence approx 0.2%	Prevalence >3%
Rapid onset of the disease*	Slow onset
Mostly in young age of <40	Generally onset after age of 40
No frequency difference by sex	More frequent in female
Nutritional status – thin	Normal or obese
Environmental factors play important roles (viruses or chemicals)	Genetic factors plays important roles
Presence of islet-cell antibodies	ICA not present
Poor insulin production or total deficiency	Reduced insulin production or hyperinsulinemia
Absolute insulin deficiency	Insulin resistance or relative insulin deficiency
Good insulin sensitivity	Poor insulin sensitivity
Ketosis prone	Ketosis resistant except during infection or stress
No response to sulphonylureas	Good response to sulphonylureas

*Although the onset symptoms in IDD is abrupt, its revolution may involve an antecedent period of slowly developing autoimmune to the pancreatic B cells.

triceps skin fold thickness (TSFT) subscapular and supralic skin folds (SSSF and SSISFT) also support the importance of obesity (in particular upper body obesity) in the development of diabetes. Upper body obesity not only predicts the prevalence of diabetes mellitus but also IGT ($P<0.0001$)[3]. Abdominal fat distribution in men and women also predicts certain risk factors of macrovascular disease, such as hypertriglyceridemia and hypertension. The mechanism by which abdominal fatness increases the risk for NIDD is not clear. Adipose tissue located in the abdomen is more sensitive to lipolytic stimuli than adipose tissue elsewhere[51]. The lipolytic products, glycerol and free fatty acid (FFA), are directly delivered to the liver in the splanchnic circulation and enhance gluconeogenesis and Very Low Density Lipoprotein-Triglyceride (VLDL-synthesis)[51]; FFA also reduce peripheral glucose uptake[50]; hypertriglyceridemia increases[7].

Fat distribution rather than total fat is a better predictor for NIDD. Upper body obesity is associated with high prevalence of NIDD especially among women[14-16]. Biceps and subscapular skin fold thicknesses and waist-hip ratio are strongly associated with NIDD in many studies[17-20].

Many obese patients have frank NIDD. They are not ketosis-prone and do not require exogenous insulin for blood glucose control. Many other obese patients have IGT. The prevalence in the community increases strikingly according to lifestyle changes leading to obesity. However, while obesity may be a very important risk factor for NIDD, it is and by itself, insufficient to produce this disease. A genetic susceptibility for NIDD may be necessary for obesity to induce clinical disease[48-49]. These are the processes which now require more intensive study in Malaysian communities.

Body composition and insulin resistance

One of the metabolic features of obesity especially upper body obesity is the existence of hyperglycemia in the face of hyperinsulinemia. This means insulin's ability to influence glucose metabolism is impaired, a condition referred to as insulin resistance. With abdominal fatness cells become less sensitive to insulin[21] and insulin binding for receptors are reduced[22].

Hyperinsulinemia in the presence of normal glucose tolerance is evident in young people in Pacific Ocean communities who have high susceptibility to NIDD. Subsequently, insulin resistance occurs which leads to secondary pancreatic β-cell exhaustion[23-27]. The exhaustion leading to an abnormality of insulin synthesis or secretion may be genetically determined. Both population surveys and prospective studies of prediabetic Pima Indians indicate that insulin resistance predates the onset of NIDD[28,29]. The 'thrifty genotype' in NIDD could contribute to insulin resistance in muscle. A selective insulin resistance in muscle would have the effect of blunting the hypoglycemia that occurs during fasting but would allow energy storage in fat and liver during feeding. Both of these features could allow hunter–gatherers to have survival advantages during periods of food shortage. However, in sedentary individuals allowed free access to food, these individuals become obese with secondary insulin resistance in fat and liver. Post-prandial hyperglycemia occurs would then lead to glucose toxicity with decreased insulin secretion from β-cells[30].

Insulin resistance is recognized by diminished response to endogenous insulin (hyperinsulinemia with normal or elevated blood glucose concentration) or exogenous insulin (diabetes requiring very large doses of insulin). Such resistance may be due to changes in insulin receptors, post-receptor events, or both[31]. In obese individuals, the insulin resistance could result from impaired glucose uptake by peripheral tissues such as skeletal muscle and adipose tissue, impaired glucose uptake by the liver or increased hepatic glucose production. However, resistance to insulin action also occurs in lean individuals with NIDD. Thus it is considered that peripheral tissue insulin resistance is a characteristic of NIDD and obesity may not require to produce it[27], unless subtle increases in abdominal visceral fat have not been recognized.

The number of receptors appears to be lower in obese patients[7,13]. One theory concerning the development of insulin resistance in obese NIDD postulates that repetitive postprandial hyperglycemia initially leads to a down regulation of insulin receptors, which then results in a compensatory increase in insulin secretion to prevent glucose intolerance. With more prolonged and greater hyperglycemia, postbinding defects in insulin action then emerge. Decreases in the intracellular and plasma pools of glucose transporter may occur. Overt diabetes develops only in individuals whose pancreas is unable to meet the increased and sustained demand for insulin secretion[24].

The cellular mechanism for insulin resistance in NIDD is still poorly understood. Early reports indicated the inconsistent relationship between insulin receptor binding and diabetes. However, more recent reports have found evidence for a postbinding defect in NIDD. Increased lipolysis in the glucose-fatty acid cycle is partly responsible for the post-insulin receptor resistance. Insulin resistance in NIDD is associated with increase in VLDL-TG and decrease in HDLC. However, whether insulin resistance causes increased VLDL or, conversely, whether elevations in VLDL impair insulin action, is yet to be determined[33].

Hyperinsulinemia and associated insulin resistance with normal glucose tolerance and not impaired insulin secretion could be considered as an early phase in the development of NIDD[24,34,35]. Progression from normal to IGT is associated with a reduction in insulin sensitivity. However, glucose tolerance is mildly impaired with a further compensatory increase in insulin secretion. Syndrome X is the name given to the association of obesity, hypertension, hypertriglyceridemia, hyperuricemia and insulin resistance. It is conceivable that abdominal visceral obesity underlies most of the syndrome, and, in turn, genetic predisposition to it along with a fatty refined diet and physical inactivity. If this be the case, then greater attention to the increasing problem of NIDD, and underlying visceral obesity in Malaysia may have a useful impact on the Nation's health.

Management approach

The defective functioning of β-cells and insulin receptors are difficult to reverse. Therefore, treatment remains symptomatic correction of the metabolic defects. Exogenous insulin may not be effective due to a presence of insulin resistance. However, diet, oral hypoglycemic agents and exercise may be beneficial in obese NIDD[23,36-38]. Even so all treatment should be designed to suit individual patients in relation to ethnic groups' lifestyle, work schedule and education.

Dietary adjustment

Dietary adjustment to reduce weight is the choice for obese NIDD patients with insulin resistance. Weight loss results in an improvement in the metabolic aspects of the diabetic state of obese individuals with diabetes. In many patients, glucose, lipid, protein metabolism and insulin secretion and action are restored to normal. In others, weight loss improves the diabetic state but some metabolic derangements still persist[32]. The choice of the best diet may depend on the degree of obesity and the stage of progression of β-cell dysfunction[39].

A reduced-energy regimen should consist of 50–55% carbohydrates, 15% protein and 30–35% fats (with a high percentage of polyunsaturated fats). Obese diabetics will benefit from weight reduction because reducing body weight actually reduces high glucose levels to normal (improved glucose tolerance)[40]. Many obese NIDD patients, in the earlier stages of diabetes, tolerate weight-maintenance high-carbohydrate, low-fat diets without deterioration of glucose tolerance. However, as their insulin reserve declines, high-carbohydrate diets may further raise glucose levels, so a lower carbohydrate diet seems preferable. However, in advanced NIDD with deficiency of insulin secretion, high-carbohydrate diets especially refined carbohydrates should be avoided[39].

Diets which are high in carbohydrate and natural fiber content produce a lowering of blood glucose as well as a lowering of low-density lipoprotein cholestrol (LDLC) and triglycerides in patients with NIDD[41]. In such patients, glucose homeostasis improvement is due to increased insulin sensitivity. For obese patients with diabetes, increased fiber in the diet may also enhance satiety, thereby aiding in weight reduction. A study carried out in Oxford found that diets containing a very high proportion of beans (61% carbohydrate, 18% fat, 21% protein and 96.9 g of fibre per day) resulted in the whole of the glucose profile being lowered[41]. Delayed absorption can be achieved by delayed gastric emptying presumably by dietary fibres or by using 'swelling substances' and slow breakdown of carbohydrates[7]. Guar gum and pectin (soluble fibre) was found to delay the absorption and can be useful in NIDD.

The arteriosclerotic complications found in patients with diabetes have been attributed partly to elevated plasma lipid concentrations which are influenced by fat intake. Diets for patients with diabetes should therefore have reduced fat intake to correct the unfavourable lipid profile. Achievement of ideal weight, glycemic control, and when necessary, medical treatment of hyperlipidemias will retard the process of atherosclerosis. HMG Co-A reductase inhibitor (pravastatin), and other hypolipidemic agents such as gemfibrozil[42], and bezafibrate ·educe cardiovascular risk through the correction of 'yslipidemias[43].

Oral hypoglycemic drugs

Biguanies act to decrease absorption, inhibit gluconeogenesis, stimulate glucose conversion in muscle and fatty tissue and lower plasma lipid levels. Their action, therefore, is linked to the presence of endogenous or exogenous insulin and so they are particularly suitable for obese diabetics. The side effect of lactic acidosis is probably less with metformin than other biguanides[7].

Sulphonylureas act by stimulating β-cells to release insulin (it depends upon the existence of β-cells) and helping glucose sensitize the cells. They are useful for NIDD which cannot be controlled by diet alone. In NIDD insulin is secreted after stimulation by glucose, but its secretion is delayed and at low peak. About 30% reduction of blood glucose level will be produced by using these drugs. Since sulphonylureas increase insulin secretion, they may be relatively contraindicated in obese people with diabetes and hyperinsulinism.

Physical activities

Physical activity improves physical fitness, increases energy expenditure, helps appetite regulation, favourably influences serum lipoproteins, lowers blood pressure and, importantly, decreases the risk of coronary artery disease. Physical training can increase insulin sensitivity[42a]. However, the long-term effects on blood glucose control with exercise alone are not proven. In NIDD, since the population is often obese and sedentary, exercise would be expected to have beneficial effects in promoting weight reduction and thereby improving glucose regulation[44]. Exercise alone may have a marked effect on the long-term metabolic abnormalities of NIDD. But exercise combined with diet that produces greater effects. Moreover, the weight loss produced by exercising is more easily maintained[45,46].

Even through exercise programs may have beneficial effects for patients with diabetes in conjunction with diet or hypoglycemic agents, it is inappropriate to exercise all patients at the same level of intensity, duration and frequency[47].

Weight reduction and sulphonylurea therapy can achieve a decrease in insulin resistance. Exercise and weight reduction in obese individuals are accompanied by increased insulin receptor binding and postbinding insulin actions.

Conclusion

The changing lifestyle, particularly in respect of fatty, refined diets and decreasing physical activity are likely to be contributing to visceral obesity, insulin resistance and related phenomena in Malaysia as elsewhere. Prevention and management of NIDD require greater research and understanding of these phenomena.

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身體組成在糖尿病發病機制和處理中的作用：一個馬來西亞的展望

隨著迅速社會文化的發展和生活方式的轉變，全球糖尿病患病率有所增加。肥胖症發病率的增加和進食動物食物較多、水果青菜較少，增加了糖尿病和其它慢性退行性疾病的危險性。胰島素依賴性糖尿病 (IDD) 是由胰島素缺乏引起；而非胰島素依賴性糖尿病 (NIDD) 的主要特徵是血胰島素增多和抗胰島素性，也許會直接導致胰島素缺乏，這類糖尿病佔 90% 以上。血胰島素增多可增加血管疾病的危險，是不受歡迎的。在馬來西亞某些地區，NIDD 發病率超過 5%，葡萄糖耐量減弱達 10%。同時血糖過多發病率增加，超重 (BMI >25) 發病率增加，幾乎毫無疑問地屬腹部肥胖症。對這些病人的處理，營養是首選的，需要時可用胰島素和降血糖藥（磺基脲或雙縮胍），但用量過多也許會影響身體的組成。新的治療策略需要注意到 NIDD 腹部肥胖的根本問題，如相應的營養因素、體育活動和吸煙、飲酒等。最後作者提出了馬來西亞婦女較男子多患肥胖症和糖尿病。

Di masa ini terdapat peningkatan prevalens diabetes melitus di seluruh dunia yang berkaitan dengan perkembangan sosio-budaya dan perubahan gaya hidup yang pantas. Peningkatan prevalens keobesan dengan pengambilan produk haiwan yang tinggi dan pengambilan buah-buahan dan sayuran yang rendah, meningkatkan risiko terhadap diabetes melitus dan penyakit-penyakit degeneratif kronik yang lain. Diabetes yang bergantung pada insulin (ID) adalah disebabkan oleh kekurangan insulin, sedangkan gambaran utama diabetes yang tidak bergantung pada insulin (NIDD) yang terdapat pada 90% dari pesakit diabetes adalah hiperinsulinemia dan kerintangan insulin, yang seterusnya boleh mengakibatkan kekurangan insulin. Hiperinsulinemia tidak dikehendaki kerana ia meningkatkan risiko kejadian penyakit vaskular. Di Malaysia, prevalens NIDD di kalangan beberapa masyarakat melebihi 5% dan gangguan tolerans glukos 10%. Bersama dengan peningkatan prevalens hiperglisemia adalah peningkatan prevalens lebih berat badan (BMI>25) dan lazimnya kegemukan abdomen. Dalam hal pengurusan penyakit, pemakanan diberi keutamaan. Insulin dan dadah hipoglisemik (sulphonylurea atau biguanide) dimana perlu, boleh memberi kesan terhadap komposisi tubuh jika diambil berlebihan. Strategi terapi yang baru menekankan masalah bersangkutan dengan NIDD yang mengalami kegemukan abdoman dengan memberi perhatian kepada faktor pemakanan yang relevans, aktiviti fizikal dan faktor gaya hidup yang lain seperti merokok dan minum alkohol. Impak yang besar dari keobesan dan diabetes pada wanita Malaysia berbanding lelaki juga perlu dikemukakan.