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The Role of Obesity in Producing Type 2 Diabetes by Insulin Resistance

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Research Article

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Abstract

Obesity is a common condition due wrong eating habits and less physical activity. But it can produce serious illness like type 2 diabetes. In Malaysia 18 years and above 33.3% (5.4 million) are pre-obese and 27.2% (4.4 million) are obese. 7.2% are known to have diabetes and 8.0% are previously undiagnosed with diabetes. There is a strong relationship between obesity and diabetes mellitus. We must understand the mechanism by which obesity causes diabetes through and insulin resistance. When the fat distribution is more peripheral have more insulin sensitivity than whose fat distribution is more in the waist. The insulin resistance is caused by variety of substances like non-esterified fatty acids, glycerol, hormones, cytokines, proinflammatory markers which leads to the development of insulin resistance. The development of diabetes is a combination of the failure of β-islet cells of the pancreas and insulin resistance. There is a rising incidence of type 1 and type 2 diabetes due to obesity and weight gain. The obesity is more common in females. Obesity increases with age. Similarly, the incidence of diabetes also increases with and in male sex. Out of 219 persons 77 had normal BMI (less than 25), 83 were overweight (BMI 25 to 30) and 59 were obese (more than 30). The incidence of overweight (37.8%) and obese (26%). People who are overweight (BMI 25-30) below 40 years are 8, between 40-60 years are 36 and above 60 years are 39. The people who are obese in the 40 years age group 6, 40-60 years 23 and above 60 years 30. Incidence of overweight and obese is more in the females 72.7% and males 58.4%. Incidence of overweight among female is 42% and obese are 30%. Comparatively among male 34.4% are overweight and 24% are obese.

Keywords: Obesity; Type 2 Diabetes; Insulin Resistance; Adipokines; Leptin; Adiponectin; Resistin; Accelerator Hypothesis; Endoplasmic Reticulum; MCP-1 G-2518 Gene

Introduction

The precise mechanisms linking the diabetes and obesity remain unclear. Improved understanding will help advance identification and development of effective treatment options for obesity and diabetes. BMI has low sensitivity due to a large inter-individual variability in the percent body fat for any given BMI value, as it varies due to age, sex, and ethnicity. Asians have greater percent body fat than Africans for the same BMI. Ischemic heart disease is found to be associated with the localization of excess fat in the body adipose tissue and ectopic depots (such as muscle and liver), as well as in persons with increased fat to lean mass ratio (e.g. metabolically obese normal-weight) [1]. The main assumption of BMI guidelines is that body mass, adjusted for stature squared, is closely associated with body fatness and consequent morbidity and mortality. However, some individuals who are overweight are not overfat (eg, bodybuilders). Some people have normal BMIs but have a high percentage of their body weight as fat. Instead of BMI

the percentage body fat was measured by three methods. Body fat was measured by DXA scanners which measures body composition, tritium or deuterium dilution volume, bone mineral mass and body density were measured [2]. Among the obese pre diabetics, 42.2% had both IFG and IGT, 47.0% had isolated IFG and 10.8% had isolated IGT, 36.2%. 53.4% of the obese pre-diabetics will have family history of diabetes. Pre-diabetics who were of normal weight reported higher health-related quality of life HRQOL compared to those overweight and obese. The research shows that overweight or obese prediabetics are at greater risk of developing poor health-related quality of life. Physical activity and weight control are very important to prevent diabetes in pre-diabetics at the primary care level [3].

AIM: A study was conducted to find the incidence of diabetes mellitus among the obese people.

Material and Methods

During the heath camp conducted during a religious festival, a survey was conducted to find out the incidence of obesity among diabetic people. 213 took part in this survey of them 124 were males and 95 were females. 15 were below 40 years, in metres (kg/m2). Random blood sugar was done for all persons.

Results

Among the total 219 people 124 are male and 95 are females. Out of 219 persons 77 had normal BMI (less than 25), 83 were overweight (BMI 25 to 30) and 59 were obese (BMI more than 30). The incidence of overweight was (37.8%) and obese (26%). Incidence of overweight and obese is more in the females 72.7% and males 58.4%. 41.1% of males are normal weight but only 27.3 of females are normal weight. Incidence of overweight among female is 42% and obese are 30%. Comparatively among male 34.6% are overweight [Chart 3]. In the younger age group, the obesity is more common in males but in the older individual they are almost equal. Only 26 females had normal BMI and among them 5 had diabetes and 17 are prediabetic (Table 1). Among 40 over-weight women 12 had diabetics and 23 are prediabetic (Table 2). Out of 30 obese females 8 diabetes and 19 are prediabetic (Table 3). Incidence of diabetes in females is 25/86 and prediabetic are 59/86. Among 123 males 29 are diabetics and 61 are pre diabetic (Table 4). Out of 43 overweight males 11 are diabetic and 24 are prediabetic (Table 5) and among 29 obese males 8 are diabetic and 16 are pre diabetics (Table 6). Out of 54 males aged above 60 years 19 are diabetics and 28 are prediabetics. But in the age group of 40-60 years 10 are diabetics and 34 are prediabetic. Among 51 normal males 10 had diabetes and 34 are prediabetics (Table 7). Table 8: Showing BMI and blood sugar level in different age groups in females. Among 41 females aged above 60 years, 16 are diabetic and 18 are pre diabetic, among 19 overweight women 7 had diabetics and 9 are prediabetic and among 15 obese women 4 had diabetes and 9 are prediabetics. In females 25/86 are diabetic and 59/86 are prediabetics (Table 8). Out of 31 females in the age group 40-60 years 12 are diabetic and 18 are prediabetic. None of 25 people below 40 years with normal BMI had diabetes out 20 are prediabetic. (Table 9). Among the 36 people aged 40–60 yeas overweight people 8 had diabetes out 23 are prediabetic (Table 10) Out of 30 obese people older than 60 years 8 had diabetes out 18 are prediabetic (Table 11).

Female BMI < 25				
Age	**< 40 years**	**40 – 60 years**	**> 60 years**	**Total**
<5.5	4	0	0	4
5.5-8	13	1	2	16
8.1-10	1	0	0	1
>10	0	0	5	5
TOTAL	18	1	7	26

Table 1: Blood sugar level and BMI level among normal females.

	Female BMI 25 - 29			
Age	**<40 years**	**41-60 years**	**>60 years**	**Total**
< 5.5	0	2	3	5
5.5 -8	2	9	5	16
8 -10	1	2	4	7
>10	0	5	7	12
Total	3	18	19	40

Table 2: Blood sugar level and BMI level among overweight females.

Female BMI > 30				
Age	**< 40 years**	**40 – 60 years**	**> 60 years**	**Total**
<5.5	0	1	2	3
5.5-8	1	5	7	13
8.1-10	1	3	2	6
>10	1	3	4	8
Total	3	12	15	30

Table 3: Blood sugar level and BMI level among obese females.

Male BMI < 25				
Age	**< 40 years**	**40 – 60 years**	**> 60 years**	**Total**
<5.5	1	5	1	7
5.5-8	5	11	7	23
8.1-10	1	6	4	11
>10	0	3	7	10
Total	7	25	19	51

Table 4: Blood sugar level and BMI level among normal males.

Male BMI 25 - 30				
Age	**< 40 years**	**40 – 60 years**	**> 60 years**	**Total**
<5.5	1	3	4	8
5.5-8	4	10	4	18
8.1-10	0	2	4	6
>10	0	3	8	11
Total	5	18	20	43

Table 5: Blood sugar level and BMI level among overweight males.

Male BMI > 30				
Age	**< 40 years**	**40 – 60 years**	**> 60 years**	**Total**
<5.5	1	2	2	5
5.5-8	1	3	7	11
8.1-10	1	2	2	5
>10	0	4	4	8
TOTAL	3	11	15	29

Table 6: Blood sugar level and BMI level obese males.

Male				
Age	**< 40 years**	**40 – 60 years**	**> 60 years**	**Total**
Blood sugar < 5.5				
BMI <25	5	11	7	23
25 – 30	1	3	4	8
> 30	1	2	2	5
Total	7	16	13	36
Blood sugar 5.5-8				
BMI <25	5	11	7	23
25 – 30	4	10	4	18
> 30	1	3	7	11

Total	10	24	18	52
Blood sugar 8.1 - 10				
BMI <25	1	6	4	11
25 – 30	0	2	4	6
> 30	1	2	2	5
Total	2	10	10	22
Bloods sugar > 10				
BMI <25	0	3	7	10
25 – 30	0	3	8	11
> 30	0	4	4	8
Total	0	10	19	29

Table 7: Showing BMI and blood sugar level in different age groups in males.

Female				
Age	**< 40 years**	**40 – 60 years**	**> 60 years**	**Total**
Blood sugar < 5.5				
BMI <25	4	0	0	4
25 – 30	0	2	3	5
> 30	0	1	2	3
Total	4	3	5	12
Blood sugar 5.5-8				
BMI <25	13	1	2	16
25 – 30	2	9	5	16
> 30	1	5	7	13
Total	16	15	14	45
Blood sugar 8.1 - 10				
BMI <25	1	0	0	1
25 – 30	1	2	4	7
> 30	1	3	2	6
Total	3	5	6	14
Bloods sugar > 10				
BMI <25	0	0	5	5
25 – 30	0	5	7	12
> 30	1	3	4	8
Total	1	8	16	25

Table 8: Showing BMI and blood sugar level in different age groups in males.

	BMI <25		
Age	< 40 years		
	Male	Female	Total
<5.5	1	4	5
5.5-8	5	13	18
8.1-10	1	1	2
>10	0	0	0
TOTAL	7	18	25

Table 9: Showing incidence of diabetes and overweight in normal people below 40 years.

	BMI 25- 30		
Age	40 – 60 years		
	Male	**Female**	**Total**
<5.5	3	2	5
5.5-8	10	9	19
8.1-10	2	2	4
>10	3	5	8
Total	18	18	36

Table 10: Showing incidence of diabetes and overweight people 40 -60 years.

	BMI > 30		
Age	>60 years		
	Male	**Female**	**Total**
<5.5	2	2	4
5.5-8	7	7	14
8.1-10	2	2	4
>10	4	4	8
Total	15	15	30

Table 11: Showing incidence of diabetes and overweight in normal people more than 60 years.

Discussion

Interconnected nutritional, hormonal, and neural regulatory systems tightly control the energy balance and metabolic homeostasis. Increased incidence of obesity among all age groups and both sexes, decreased physical activity, fast food and urbanization are identified as the cause for raising type 2 diabetic patients. This finding is important as it will allow health planners to make rational plans and reallocate health resources accordingly [4]. For the past 20 years there is global increased incidence of obesity which explains the dramatic increase in the incidence and prevalence of type 2 diabetes. In US, over a third (34%) adults are obese (defined as BMI >30 kg/m2), and over 11% of people aged more than 20 years have diabetes [5]. A prevalence projected to increase to 21% by 2050 [6]. Diabetes mellitus (DM) is a chronic disorder which alters carbohydrate, protein, and fat metabolism. Type 2 diabetes has a different pathophysiology and aetiology as compared to type 1 diabetes. Type 2 diabetes is due to the absence or decreased insulin secretion due to either the progressive or marked inability of the β-Langerhans islet cells of the pancreas to produce insulin, or due to defects in insulin uptake by peripheral tissue. The "accelerator hypothesis" was proposed by Wilkin [7] is considered as most accepted theory which demonstrates the association between body mass and type 1 diabetes. This theory suggests that the increasing body weight in younger people increases the risk of developing type 1 diabetes. There is an inverse relationship between body mass index and age at diagnosis. Whenever young children gain more weight, diabetes can be diagnosed earlier. This can be explained by the fact that obesity accelerates insulin resistance, leading to the development of type 1 diabetes in individuals who are predisposed genetically to diabetes. There is significant increase in the prevalence of overweight among children with type 1 diabetes, from 12.6% in the 10 years period 1979–1989 to 36.8% in the period 1990–1998 [8]. Recent studies suggest that abdominal fat causes fat cells to release 'pro-inflammatory' substances, that makes the body less sensitive to the insulin. It disrupts the function of insulin responsive cells and their ability to respond to insulin. This is known as insulin resistance which is an important factor producing type 2 diabetes. Especially having excess abdominal fat (i.e. a large waistline) which is known as central or abdominal obesity is high-risk form of obesity. In obese persons, cells of fat tissues must process more nutrients than they can manage. It produces an inflammation that releases a protein called cytokines. Cytokines block the signals of insulin receptors causing the cells to become resistant to insulin. As insulin resistance develops the body cannot convert the glucose into energy and leads to persistently high blood glucose level. Improved understanding of cytokine and insulin resistance will help to identification and development of effective treatment. In obesity there is increased amount of non-esterified fatty acids, glycerol, hormones, cytokines, proinflammatory markers, and other substances which produces insulin resistance. The development of diabetes is inevitable if the failure of β-islet cells of the pancreas is associated with insulin resistance. Weight gain and body mass are important to the rising incidence of type 1 and type 2 diabetes [9]. More weight accelerates insulin resistance,

leading to the development of type 1 diabetes in individuals who are predisposed genetically to diabetes. Significant increase in the prevalence of being overweight in children with type 1 diabetes, from 12.6% in the period 1979–1989 to 36.8% in the period 1990–1998 [10]. The increased prevalence of obesity these days has drawn attention to the worldwide significance of this problem [11]. Insulin level in type 2 diabetes may be high, yet it is not enough to normalize the level of glycemia [12]. Type 2 diabetes and obesity can be associated with insulin resistance. Most obese individuals, despite being insulin resistant, may not develop hyperglycaemias as Pancreatic β-cells release adequate amounts of insulin to overcome insulin level reductions under normal circumstances, thus maintaining normal blood glucose level [13]. To develop insulin resistance and obesity, thereby producing type 2 diabetes, β-cells should not be able to compensate fully for decreased insulin sensitivity. The non-esterified fatty acids (NEFAs) secreted from adipose tissue in obese people may lead to the hypothesis that insulin resistance and β-cell dysfunction can be interlinked [14]. The nutrient overload and positive net energy balance causes resistance to the normal action of insulin. Insulin resistance produces increased free fatty acid (FFA) flux from adipose tissue to non-adipose tissues, resulting from abnormalities of fat metabolism. Adverse metabolic consequences of increased FFA flux and lipid accumulation produces dyslipidaemia, impaired hepatic and muscle metabolism, decreased insulin clearance, and impaired pancreatic -cell function. In addition, there is increasing appreciation that obesity and insulin resistance are chronic inflammatory status. There is growing evidence that FFAs activate the NFB inflammatory pathway through action on the IKK kinase, thereby increasing pro-inflammatory response [15]. The endoplasmic reticulum is responsible for processing protein and fat. Overeating produce excess stress on the endoplasmic reticulum (ER) inside the cell. When there is excess nutrient inside the ER than it can process, it sends out signal forcing the cell to supress the insulin receptors on the cell surface. This results in insulin resistance and persistently higher concentrations of glucose in the blood. A link was identified between the activation of the inflammatory and stress kinase JNK and inhibition of insulin receptor signalling via phosphorylation of the insulin receptor substrate (IRS-1) [16]. When adiposity increases the risk for developing insulin resistance is also increases producing type 2 diabetes, as 80% of type 2 diabetic patients are found to be obese. This increase in glycemia leads to deterioration in β-cell function and insulin resistance resulting in Type 2 diabetes. If the molecular basis for the β-cell dysfunction and death, and muscle and hepatic insulin resistance is identified new therapies can be developed to correct those defects. Triglyceride storage at various sites is increased due to increased intake of high fatty diets which leads to obesity. Obesity in turn leads to tissue dysfunction, including insulin resistance and cell death because of chronic exposure of tissues to elevated lipids level and resultant accumulation of toxic by-products of lipid metabolism. Adipose cells carry various hormones like adipokines, Leptin, adiponectin (also Acrp30) and resistin, and proinflammatory cytokines such as interleukin (IL)-6 and tumour necrosis factor (TNF). Most of these peptides secreted by adipocyte regulate the metabolism of lipid and glucose [17]. These peptides play a prominent in the of development insulin resistance and diabetes [18]. Leptin levels are increased, and adiponectin levels are decreased in insulin resistant, obese type 2 diabetic patients. So, obesity leads to a state of leptin resistance, and adiponectin deficiency [19]. The transmembrane protein STAMP2 and double stranded RNA dependent protein kinase PKR are the significant molecules and pathways which are found to be key modulators of chronic metabolic inflammation, insulin sensitivity and glucose metabolism in obesity [20]. Lipokine, is a lipid natured hormone, has useful actions on glucose and lipid metabolism [21]. Some studies have demonstrated that in obesity aP2 is released from adipocytes and its levels are significantly increased [22]. Therapeutic targeting of both these molecules will be useful for the management of obesity, diabetes, and hyperlipidaemia. Obesity is one of the important factors in the development of metabolic diseases like type 2 Diabetes, hypercholesterolemia. Adipose tissue affect metabolism by secreting hormones, glycerol, leptin, cytokines, adiponectin, and other proinflammatory substances, and by releasing NEFAs. All these substances are increased in obese individuals [23]. The most important factor affecting insulin insensitivity is the release of NEFAs. Increased release of NEFAs is observed both in type 2 diabetes and in obesity, and it is associated with insulin resistance [24]. Shortly after an acute increase of plasma NEFA levels in humans, insulin resistance will develop. When the level of plasma NEFA decreases, as in the case with antilipolytic agent use, peripheral insulin uptake and glucose metabolism will be improved [25]. Insulin resistance is associated with body mass index whenever there is weight gain. People whose fat distribution is more peripheral (ie. pelvis and limbs) have more insulin sensitivity than the people whose fat distribution is more central (ie, in the abdomen and chest area) [26]. In obesity, insulin sensitivity, as well as the modulation of β-cell function, decreases [27]. When there is obesity the adipose will release increased amounts of glycerol ,non-esterified fatty acids, pro-inflammatory cytokines, hormones and other factors that are involved in the development of insulin resistance. When insulin resistance is accompanied by dysfunction of pancreatic islet beta-cells - the cells that release insulin causes type 2 diabetes. This knowledge is helpful in exploration of the molecular and genetic basis of type 2 diabetes and new approaches to its prevention and treatment [28]. Experimental VMH lesion mediated model of obesity and insulin resistance has been found to be associated with

vagal hyperactivity and proliferation of islet cells, particularly β-cells [29]. Thus, it is plausible that increased vagal input associated with diet-induced obesity might also contribute to extensive innervation with increased β-cell mass and alteration in the insulin sensitivity. Moreover, another study showed that MCP-1 G-2518 gene variant decreased the risk of type 2 diabetes. Apart from CCL2/MCP-1, several other chemokines such as CCL5, C-X-C motif chemokine ligand 5 (CXCL5) and CXCL14 were also involved in adipose tissue macrophage infiltration and obesity-induced insulin resistance [30-32]. Moreover, circulating IL-18 levels have been observed to be increased in obese subjects and reduced with weight loss and its overexpression enhanced insulin resistance in a rat model of metabolic syndrome [33,34]. Obesity and diabetes are linked to an increased prevalence of dyslipidaemia. Abdominal fat is more lipolytic than subcutaneous fat, also does not respond easily to the antilipolytic action of insulin and intra-abdominal fat is more important in causing insulin resistance, and leads to diabetes mellitus. The body fatty acid release is higher in obese subjects as compared to lean subjects because of their greater fat mass [35].

All countries are facing the challenge of increasing incidence of diabetes, loss of productivity and death. Lifestyle changes promote excessive energy intake and reduced energy expenditure. This causes increased prevalence of obesity and type 2 diabetes in developed and developing countries over the past few decades. It is very important to take early action to contain an epidemic of obesity and associated diabetes. Future research must be directed towards the pathogenesis of the coexistent condition of obesity and diabetes type II and he newer approaches to their pharmacological and surgical management. The link between obesity and type 2 diabetes must be found which will help us to find effective and cost-effective interventions for both conditions. The rapid and marked socioeconomic advancement has brought a significant change in the lifestyles of Malaysians in the past few decades. Dietary habit has changed due production of high calorie diet by fast-food industry and easy availability in the Supermarkets have led to changes in the dietary and meal patterns. Nowadays more families and adolescents eat rich food outside their homes. Fast food outlets are present even in small towns. These caused an increase in the consumption of highly processed foods and sugar sweetened beverages. People prefer sedentary activities like watching television, screen-based media, playing video game, using mobile phones than doing physical activity. Healthy food and regular physical exercise are the easiest choice to manage obesity. People can limit calorie intake from total fats and sugars and increase intake of fruit and vegetables, legumes, whole grains, and nuts; and must engage in regular physical activity (60 minutes a day for children and 150 minutes per week for adults).It requires a political will and the relevant Ministries should make the food industry to play a major role in promoting healthy diets. The supply of vegetables and fruits. They must be available freely and at affordable price to all consumers. The fat, sugar and salt content of processed foods must be reduced. Restricting the marketing of foods high in sugars, salt, and fats to the general population and to those foods aimed at children and teenagers. Large share of the marketing of unhealthy foods is done through the Mass media such as newspapers and television. Most of the advertisements influence children's choice of food and its consumption. Hence there must be some regulation for this type of advertisements. WHO has recommends that children and young people aged 5-17 years must be encouraged at least 60 minutes of moderate to vigorous-intensity physical activity every day. At least three times a week, vigorous-intensity activity can be incorporated to strengthen muscle and bone [36].

Conclusion

The incidence of diabetes is higher among obese people. The incidence of prediabetics are more in the 40-60 years group. If dietary restrictions are followed and increased physical activity will delay the onset of diabetes or can prevent it. Obesity is not just an individual problem. It is a common problem involving all the people in all countries and should be tackled effectively. Effective prevention and management of obesity will require an integrated approach, involving actions in all sectors of society.

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