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Diabetes and obesity are amongst the biggest scourges of the twenty-first century – the twin horsemen of the apocalypse. Until 50 years ago diabetes was considered to be a disease of developed countries and commonest in Europids. In the 1960s it became clear that diabetes was very common in certain other groups – Pima Indians and Nauruans in the Pacific. In both these groups it was associated with rapid improvement in economic status. Since that time there has been an inexorable increase in the number of people with diabetes world-wide. In some areas this rise started later than others, for example rural sub-Saharan Africa, but now there are few parts of the world which are spared. By far the majority of this rise has been in type 2 diabetes, although for unknown reasons there has been an increase in type 1 diabetes as well. In 1990 there were approximately 100 million people with diabetes. This had risen to almost 250 million by 2007 and is predicted, conservatively, to increase further to 350 million by 2030. In addition, there are about the same number of people with impaired glucose tolerance, many of whom will develop diabetes in the future.

Several factors have contributed to this epidemic rise in prevalence. These are largely related to lifestyle changes. Ethnicity and family history contribute – thus people of South Asian origin and Afro-Caribbeans have a much greater susceptibility than Europids – but only if their lifestyle changes. The latter encompasses obesity as well as decreased physical activity and increasing urbanization.

The major problem is, of course, obesity. This has shown a parallel rise world-wide with that found for diabetes. In the United States a recent survey showed that 26% of adults were obese (body mass index, BMI > 30 kg/m2) with highest rates in the 50–59 year age group and in non-Hispanic black women (39%). Other countries are showing similar rates, with the United Kingdom and Australia rapidly catching up. This is not however restricted to the economically advantaged world. Obesity rates are rising in all countries and there is now a U-curve for BMI in many countries, with malnutrition and underweight still rife at the same time as obesity rates are rising. Of even greater concern are obesity rates in children, which have also risen dramatically – up to 20% in many countries – and are now associated with the appearance of type 2 diabetes in children and adolescents, a previously unknown phenomenon. The costs are crippling – both economically and to the individual. The National Health Service already spends £4.2 million a year on the direct effects of obesity and £15.8 million on the wider costs.
This is predicted to rise to £50 million by 2050. It has also been calculated that 58% of the rise in type 2 diabetes can be attributed to obesity.

Obesity is linked to diabetes through insulin resistance, which is directly related to weight. Susceptible people may have sufficient insulin secretion to maintain normoglycaemia if they retain sensitivity to insulin. However, when they become less insulin sensitive through increased weight and decreased activity then hyperglycaemia develops and eventually diabetes supervenes. The distribution of weight is also important with central adiposity more damaging than peripheral fat deposition.

The editors of the current book have recognized the importance of the link between obesity and diabetes – this indeed is the second edition. They have assembled an international team of experts to discuss many of the key aspects of type 2 diabetes, obesity and their treatment. The discussions range from basic pathophysiology and genetics to behavioural change, the role of bariatric surgery and childhood obesity to the impact of ethnicity and obesity and employment. I recommend the volume to you strongly.

Sir George Alberti
Contributors

Anthony Barnett
Birmingham Heartlands Hospital
Undergraduate Centre
Bordesley Green East
Birmingham
B9 5SS UK

Iain Broom
The Robert Gordon University
School of Life Sciences
St. Andrew Street
Aberdeen
AB25 1HG UK

Ian Campbell
Park House Medical Centre
61 Burton Road
Carlton
Nottingham
NG4 3DQ UK

Tahseen Chowdhury
Department of Metabolic Medicine
The Royal London Hospital
Whitechapel Road
London
E1 1BB UK

Carlton Cooke
Carnegie Research Institute
Leeds Metropolitan University
Headingley Campus
Leeds
LS6 3QS UK

Paul Gateley
Carnegie Research Institute
Leeds Metropolitan University
Headingley Campus
Leeds
LS6 3QS UK

Susan A Jebb
MRC Human Nutrition Research
Elsie Widdowson Laboratory
Fulbourn Road
Cambridge
CV1 9NL UK

Laura Johnson
Health Behaviour Unit
Department of Epidemiology and Public Health
University College London
2–16 Torrington Place
London
WC1E 6BT UK

David Kerrigan
Gravitas
Murrayfield Hospital
Holmwood Drive
Wirral
CH63 1AU UK

Sudesh Kumar
Warwick Medical School
University of Warwick
Coventry
CV4 7AL UK
Victor Lawrence
Department of Diabetes and Endocrinology
St Mary’s Hospital
Parkhurst Road
Newport, Isle of Wight
PO30 5TG UK

Joana Lindstrom
Department of Public Health
Diabetes and Genetic Epidemiology Unit
University of Helsinki
Helsinki
Finland

Konstantinos Lois
Clinical Sciences Research Institute
Clinical Sciences Building
University Hospitals of Coventry and Warwickshire
Clifford Bridge Road
Coventry
CV2 2DX UK

Krys Matyka
Clinical Sciences Research Institute
Clinical Sciences Building
Walsgrave Hospital
Clifford Bridge Road
Coventry
CV2 2DX UK

John Pinkney
Gravitas
Murrayfield Hospital
Holmwood Drive
Wirral
CH63 1AU UK

Diana Raskauskiene
Department of Endocrinology
School of Medicine
Keel University
Thornburrow Drive
Hartshill
Stoke-on-Trent
ST4 7QB UK

Catherine Rolland
School of Life Sciences
St. Andrew Street
Aberdeen
AB25 1HG UK

Ponnusamy Saravanan
Clinical Sciences Research Institute
Warwick Medical School
University of Warwick
Coventry
CV4 7AL UK

Jayadave Shakher
Diabetes and Endocrinology
Birmingham Heartlands Hospital
Bordesley Green East
Birmingham
B9 5SS UK

Karri Silventoinen
Department of Public Health
Diabetes and Genetic Epidemiology Unit
University of Helsinki
Helsinki
Finland

Jaakko Tuomilehto
Department of Public Health
Diabetes and Genetic Epidemiology Unit
University of Helsinki
Helsinki
Finland

Brent Van Dorsten
Department of Rehabilitation Medicine
University of Colorado Health Science Center
Box 1650 MS F-713
Anschutz Outpatient Pavilion
Aurora
CO 80010 USA
Jonathan Webber
Diabetes Centre
Selly Oak Hospital
Raddlebarn Road
Birmingham
B29 6JD UK

John Wilding
University Hospital Aintree
Longmoor Lane
Liverpool
L9 7AL UK

Nerys Williams
12 Brueton Avenue
Solihull
West Midlands
B91 3EN UK
1

Changing epidemiology of obesity – implications for diabetes

Jonathan Webber
University Hospital Birmingham NHS Foundation Trust, Birmingham, UK

1.1 Introduction

There is a global epidemic of obesity [1] and the enormous implications for diabetes of this epidemic are now clear [2,3]. A large number of co-morbidities are associated with obesity, but it is type 2 diabetes that is most closely linked with increasing adiposity [4] and even within the normal weight range diabetes prevalence begins to rise with increasing adiposity [5,6]. There are currently about 110 million patients with diabetes on a worldwide basis, with this number projected to increase to 180 million by 2010 [7]. This will clearly have major economic implications with diabetes consuming ever higher proportions of healthcare budgets [8]. Being overweight or obese with an abdominal fat distribution probably accounts for 80–90% of all patients with type 2 diabetes [9].

1.2 Assessment of obesity in epidemiological studies

Most current epidemiological studies of body weight use body mass index (BMI) to define degrees of obesity. BMI is calculated as the subject’s weight in kilograms divided by the square of their height in metres (kg/m²). Cut-offs for underweight, normal weight, overweight and obesity are shown in Table 1.1.

BMI correlates well with total adiposity [10] and with morbidity and mortality from many diseases [4], although for a number of co-morbidities, including type 2 diabetes,
the relationship is closer with abdominal body fat distribution than total body fat [11]. In epidemiological studies intra-abdominal fat is most commonly estimated using measurements of waist and hip circumference and these can be used to identify increased risk of diabetes and other cardiovascular risk factors [12]. Worryingly, one recent study suggests there has been an increase in the prevalence of abdominal obesity in overweight subjects [13]. This would further drive up the risk of subsequent type 2 diabetes.

1.3 Prevalence of obesity

The prevalence of obesity is increasing throughout the world at an unprecedented rate. To be a healthy BMI, as defined by the World Health Organization (WHO), is now to be in a minority in much of western Europe as well as the United States. Indeed, in many developing countries overweight and obesity are now so common that they are replacing more traditional problems such as undernutrition and infectious diseases as the most significant causes of ill-health. In 1995, there were an estimated 200 million obese adults worldwide and another 18 million under-five children classified as overweight. As of 2000, the number of obese adults has increased to over 300 million. This obesity epidemic is not restricted to industrialized societies; in developing countries, it is estimated that over 115 million people suffer from obesity-related problems [1]. As the proportion of the population with a low BMI decreases, there is an almost symmetrical increase in the proportion with a BMI above 25.

The WHO Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) project compares obesity rates in 48 populations spread throughout the world [14]. In the period 1983 to 1986 these rates varied from less than 5% in Beijing in China to about 20% in Malta. Recent data suggests that the BMI distribution is moving upwards in China as in the rest of the world. From 1989 to 1997 overweight (BMI 25–29.9 kg/m²) doubled in females (from 10.4 to 20.8%) and almost tripled in males (from 5.0 to 14.1%) [15]. Some of the highest prevalence figures come from the Pacific region where in urban Samoans obesity has increased from 38.8% in men in 1978 to 58.4% in 1991 [1].

Within the developed world the United States has led the obesity epidemic. In the adult population in the United States the prevalence of obesity, as determined from the National Health and Nutrition Examination Survey (NHANES), has increased from 22.9% in the period 1988–1994 to 30.5% in 1999–2000 [16]. Corresponding increases

<table>
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<th>WHO classification</th>
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<tr>
<td>Healthy weight</td>
<td>18.5–24.9</td>
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<tr>
<td>Overweight (grade 1 obesity)</td>
<td>25–29.9</td>
</tr>
<tr>
<td>Obese (grade 2 obesity)</td>
<td>30–39.9</td>
</tr>
<tr>
<td>Morbid/severe obesity (grade 3 obesity)</td>
<td>Greater than 40</td>
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have also occurred in overweight and in morbid obesity. Self-reported data (Behavioural Risk Factor Surveillance System) from much larger numbers of subjects confirm these worrying trends in the United States [2]. Indeed, if weight gain continues at the current rate in the United States by 2008 39% of the population will be obese [17]. The overall data on obesity prevalence masks other differences, including higher rates of overweight and obesity in non-Hispanic black women and in a number of minority ethnic groups. In the United Kingdom a number of surveys have documented the changes in obesity from 1980 to the current day [18] (Figure 1.1). There has been a tripling in obesity prevalence even in this relatively short period of time, with the likelihood that the UK rates will continue to rise to attain those already existing in the United States.

The age of onset of obesity is getting progressively younger [19]. This is reflected in the trends in overweight and obesity in children. In the United States the prevalence of overweight (defined as at or above the 95th centile of BMI for age) increased from 10.5 to 15.5% of 12 to 19-year olds between 1994 and 2000 and in the 2–5-year age group period the increase was from 7.2 to 10.4% in this 6 year time-span [20]; in England 9.0% of boys aged between 4 and 11 years were overweight in 1994 compared with 5.4% in 1984 [21]. The corresponding figures for girls were 13.5% (1994) and 9.3% (1984). Further recent increases were described in a recent Department of Health publication [22].

Though not all obese children become obese adults, a considerable proportion will do so [23]. The continuing rise in childhood obesity is likely to lead to a massive increase in the prevalence of those co-morbidities linked to obesity.

1.4 The epidemiological link between obesity and diabetes

The link between obesity prevalence and rates of diabetes in different populations was demonstrated by West with an increase in the prevalence of type 2 diabetes as the
population becomes more obese [24] (Figure 1.2). Whilst there are changes in the incidence of type 1 diabetes, it is type 2 diabetes that is largely responsible for the global epidemic of diabetes.

Within populations there is clear evidence of a strongly positive relationship between obesity and the risk of diabetes. Data in the United States from the Health Professionals’ Follow-up Study in men [5] and the Nurses’ Health Study in women [6] graphically illustrates the increasing risk of diabetes that obesity brings (Figure 1.3). Compared with those of a BMI less than 21, women with a BMI greater than 35 had a 93-fold excess risk of developing diabetes. The risk of developing type 2 diabetes rises progressively with increasing adiposity (whether assessed by BMI, or percentage of ideal body weight). Data from NHANES shows that for each kilogram increase in weight of the population the risk of diabetes increases by 4.5% [25]. More recent examination of diabetes trends in the United States showed an even steeper increment of diabetes risk with weight gain, with a 9% increased risk of diabetes for each kilogram of body weight gain [26]. Whether this large difference is a real phenomenon, or is explained by increased public awareness of diabetes is not clear, as the later study depended on telephone surveys.

Where populations have changed their lifestyle and become more obese (e.g. Pima Indians of Arizona, Micronesian Nauruan Islanders) an epidemic of type 2 diabetes has followed on. Groups that were previously lean and had a low incidence of diabetes have become obese diabetics. Eighty per cent of adult Pima Indians are now obese and 40% of this population now has type 2 diabetes [27]. In comparison, a genetically almost identical Pima Indian population in Mexico has been described who are lean and
whose incidence of type 2 diabetes is virtually zero [28]. The importance of obesity in the development of diabetes is clearly demonstrated.

Amongst patients with type 2 diabetes excess adiposity is almost the rule. In the Diabetic Clinic in Dundee about 80% of patients attending are either overweight or obese [29]. Increasing obesity in the general population is now reflected in patients with diabetes. Of those patients newly presenting with diabetes in a clinic in Minnesota in the 1970s 33% were obese, whereas 49% of those diagnosed in the late 1980s were obese [30]. Thus, not only are we likely to see more patients with diabetes, but also to see more obese patients amongst our diabetic patients with the additional difficulties that accompany their clinical management.

In tandem with the rise in childhood obesity there is now a marked rise in type 2 diabetes in children and adolescents. There has been a 10-fold increase in type 2 diabetes amongst children between 1982 and 1994 in the United States [31]. Diabetes in this age group is clearly linked with obesity, although genetic and environmental factors also play a role with many such subjects having a family history of type 2 diabetes and belonging to minority populations [32]. In place of type 1 diabetes type 2 diabetes may soon become the more common form of childhood diabetes [33].

1.5 Factors modifying the relationship between obesity and diabetes

A large number of factors influence the relationship between obesity and diabetes and many of them are closely inter-related (Table 1.2). That obesity on its own is not sufficient to cause diabetes is apparent from the observation that 20% of patients with
type 2 diabetes are not obese and even in the highest risk group with high BMI and high waist–hip ratio over 80% will escape type 2 diabetes [6]. Other factors include body fat distribution, duration of obesity, weight gain, age, physical activity, diet, the in utero environment, infant feeding practices, childhood stunting and genetic factors. Methodological issues are also important in examining the relationship between obesity and diabetes. Some of the observed increase in diabetes prevalence attributed to obesity could be related to more awareness and detection of type 2 diabetes, rather than a true increase in numbers (previous Diabetes UK estimates are that 50% of patients do not know they have type 2 diabetes). The change in the diagnostic criteria for diabetes introduced by the American Diabetes Association in 1997, with less use of the oral glucose tolerance test and more emphasis on the fasting glucose, appear to underestimate the prevalence of diabetes in obese subjects who may have a relatively normal fasting blood glucose in the presence of a high post-load glucose [34].

Abdominal obesity may be an even better predictor of the development of type 2 diabetes than BMI [11]. The predictive value of high waist–hip ratios and high waist circumferences in mediating the risk of diabetes appears to be of most importance in those in the highest quintile of these measures [5] and perhaps in leaner subjects. For a given BMI many Asian populations have a much higher risk of type 2 diabetes, even at a BMI well within the normal range [35]. WHO is currently studying the use of a more limited range of normal BMI (18.5–22.9 kg m\(^{-2}\)) in these groups together with use of waist circumference [36].

The duration of exposure to obesity is an important modulator of the risk of diabetes. In Pima Indians, subjects’ whose BMI was greater than 30 kg/m\(^2\) for more than 10 years had over twice the risk of type 2 diabetes compared with those who had been obese for less than 5 years [37]. The epidemic of childhood obesity allied with the influence of obesity duration suggests both increasing frequency of diabetes and its earlier onset.

Weight gain during adult life acts in addition to BMI per se to modify the risk of diabetes. In the Health Professionals’ Follow-up Study men who gained more than 13.5 kg over the 5 years of the study had a 4.5-fold increased risk of diabetes in comparison with those men who remained within 4.5 kg of their weight at entry to the study [5]. Similar findings apply to women as described in the Nurses’ Health Study where the relative risk of diabetes was 2.7 in those who gained 8–10.9 kg compared with those who were weight stable over a 14-year period [6].

<table>
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<td>Infant feeding practices</td>
<td>Age</td>
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<td>Duration of obesity</td>
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<td>Dietary composition</td>
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Alongside the epidemic of childhood obesity and diabetes there is also an epidemic of diabetes related to the ageing population. The prevalence of type 2 diabetes increases progressively with age peaking at 16.5% in men and 12.8% in women at age 75–84 years [38]. Obesity rates plateau about 20 years earlier [18], but the age-related increases in total body fat and visceral adiposity make BMI a less good marker of adiposity in older age groups. Indeed, many normal weight elderly men and women are at high risk of type 2 diabetes due to increased visceral abdominal fat [39]. In the United Kingdom it is projected that due to population ageing by 2036 there will be 20% more cases of type 2 diabetes than in 2000 [8].

Decreasing levels of physical activity are undoubtedly implicated in the epidemic of obesity, but physical activity also has independent protective effects on the risk of diabetes. In the British Regional Heart Study, whilst BMI was the dominant risk factor for diabetes, men who engaged in moderate levels of physical activity had a substantially reduced risk of diabetes, relative to the physically inactive men, even after adjustment for age and BMI [40]. Similar data in women demonstrate a relative risk of type 2 diabetes of 0.67 in those who engaged in vigorous exercise at least once a week compared with women who did not exercise weekly [41]. At least in terms of reducing the risk of type 2 diabetes it is probably better to be overweight and physically active, than to be normal weight and inactive [42].

Dietary factors appear to have effects independent of those of obesity on the development of type 2 diabetes. Increasing fat in the diet is associated with both obesity and the development of diabetes [24], but much of this link is explained simply by the high energy intake that accompanies high fat diets. However, some populations with high fat diets (e.g. Eskimos and the Japanese) have a relatively low prevalence of diabetes compared with that expected from their obesity rates and this may be explained by a high intake of omega-3 polyunsaturated fatty acids [43]. A large prospective study of diet in women aged 34–59 years without diabetes at baseline and followed for 14-years found that total fat intake was not associated with risk of type 2 diabetes, but for a 5% increase in energy from polyunsaturated fat, the relative risk was 0.63 and for a 2% increase in energy from trans fatty acids the relative risk was 1.39 [44]. The authors estimated that replacing energy derived from trans fatty acids with polyunsaturated fat would lead to a 40% lower risk of type 2 diabetes. Alongside concerns about dietary fat, there is also evidence that the ready availability of sugar-sweetened drinks may contribute to obesity and diabetes [45]. In this study weight gain and greatest risk of diabetes were seen in those subjects with the highest consumption of sugar-sweetened soft drinks per day.

Whilst the vast majority of studies either show diabetes rates rising as obesity prevalence climbs, or project such a rise in diabetes from the observed obesity prevalence, one Swedish population survey has not demonstrated this [46]. From 1986 to 1999 the mean BMI in adults in northern Sweden increased from 25.3 to 26.2 kg/m² and the prevalence of obesity rose from 11 to 15%. However, in spite of the marked increase in obesity there was no increase in the prevalence of known diabetes. Dietary factors may account for some of this discrepant finding, with the diet over this period containing less saturated fat and having a lower glycaemic index. One additional
observation was a decrease in waist–hip ratio (representing reduced visceral adiposity), perhaps also contributing to the absence of a BMI effect on diabetes. Findings such as these may mean that the gloomy picture of the diabetes epidemic painted by many authors is not quite as inevitable an outcome as projected.

In contrast, data from Australia show a dramatic increase in diabetes over the last 20 years, with a doubling of diabetes prevalence to its current value of 7.4% [47]. An additional 16.4% had abnormal glucose tolerance. Whilst obesity rates in this population have increased, neither obesity nor changes in the age profile of the population fully explain the extent of the diabetes epidemic. It is likely that some of the other factors discussed above, including body fat distribution, duration of obesity, dietary composition and physical activity account for this adverse pattern.

Currently there is much interest in the concept of social networks and the local neighbourhood as factors influencing the susceptibility to obesity and diabetes. Amongst participants of the Framingham Heart Study obesity appeared clustered in communities and in groups of friends [48]. One of the many factors that social networks share is their local environment. This environment includes resources for physical activity and for healthy eating. Exercise-friendly neighbourhoods are those with safe, walkable streets, parks and public gym facilities. In terms of healthy eating, examples of positive factors include ready availability of fruits and vegetables. A study looking at the relationship between local area facilities and insulin resistance (as measured by fasting insulin concentrations in those not known to have diabetes) found that greater physical activity resources were associated with lower insulin resistance with a similar inverse relationship for healthy food [49]. There are great opportunities to target obesity and diabetes prevention by more recognition of and investment in the local environment [50].

Whilst obesity is clearly important, other factors appear to influence the susceptibility both to weight gain and to the development of diabetes. The ‘thrifty’ gene hypothesis [51] suggests that the obese-type 2 diabetes mellitus genotype may have had some survival advantage, perhaps by favouring fat storage at times when food was abundant, so leading to improved survival during famines. However, this hypothesis remains an epidemiological explanation, with the exact genetic factors remaining unclear and no prospective data showing a survival advantage in subjects felt to have a thrifty genotype.

1.6 Early life influences on obesity and diabetes

Until relatively recently it was not felt that the in utero environment would be of any great significance in the later causation of obesity and type 2 diabetes. However, long-term follow-up of cohorts of small for gestational age babies, demonstrated an increased risk of later life type 2 diabetes and heart disease [52]. The ‘thrifty’ phenotype hypothesis generated from this and similar data, proposes that the epidemiological associations between poor fetal growth and the subsequent development of type 2 diabetes results from the effects of poor nutrition in early life, which produces permanent changes in glucose and insulin metabolism. These changes lead to reduced
insulin secretion and increased insulin resistance and hence predispose to later type 2 diabetes.

Whether the critical factor for the development of childhood obesity and insulin resistance is in utero growth restriction per se is not clear. Rapid infancy weight gain, which may follow fetal growth restriction, also appears to be an important risk factor for the development of childhood obesity and insulin resistance [53]. Thus, rapid catch-up weight gain can lead to the development of insulin resistance, as early as 1 year of age, in association with increasing accumulation of central abdominal fat mass. Childhood stunting is another adverse early life phenomenon that affects later susceptibility to obesity and probably also to diabetes. Stunting remains common in lower income countries. Surveys in a number of countries show a significant association between stunting and overweight status in children in many countries [54]. With the transition from a lower income developing country to a more affluent developed one it is likely that the increased early stunting-mediated susceptibility to obesity will be compounded by later economic and social changes driving up obesity and diabetes rates.

At present there is more concern about large for gestational age babies and the later health consequences of this. One well-described group is those babies born to mothers with gestational diabetes. Maternal hyperglycaemia is proposed to influence not only fetal metabolism, but have more enduring effects throughout infancy and childhood leading to an increased risk of obesity and diabetes. This hypothesis has been supported by a large study demonstrating that increasing hyperglycaemia in pregnancy is linked with an enhanced risk of childhood obesity [55]. In this study it appeared that treatment of gestational diabetes attenuated the later risk of obesity. Longer-term follow up will be needed to show whether the type 2 diabetes risk is also reduced and how important this early metabolic imprinting is for long-term health.

1.7 Conclusions

There is no doubt that obesity is at present the major player in the increasing prevalence of type 2 diabetes. The current epidemic of obesity shows little sign of abating in most parts of the world and in contrast is still accelerating, particularly in children. Global predictions of the diabetes epidemic with 300 million patients with type 2 diabetes by 2025 are well on course [7]. Many of the factors that modify the relationship between obesity and diabetes, such as duration of obesity and physical activity levels are also changing adversely and are exacerbating the diabetes epidemic. The challenge for society is to reverse the ever-increasing prevalence of obesity.

References

REFERENCES