Prevention of cardiovascular disease: Obesity, diabetes and the metabolic syndrome

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The current obesity pandemic is expected to result in considerable downstream morbidity, mortality and incremental costs to health care systems around the world. The major metabolic complications of obesity – type 2 diabetes and the metabolic syndrome – are predicted to be particularly burdensome. Recent randomized controlled trials have demonstrated that lifestyle interventions resulting in modest weight losses are efficacious in delaying or preventing the development of type 2 diabetes in high-risk individuals. However, on a practical level, obesity prevention strategies and programs in the 'real world' have demonstrated limited effectiveness for weight reduction. It is likely that the best that can be expected from current preventive strategies, which have largely focused on modifying individual behaviour, is the prevention of further weight gain. Environmental, social, psychological and economic drivers of the obesity epidemic have, until recently, been underappreciated and underemphasized as contributors to the current pandemic. Future efforts will need to focus on these factors and pansocietal solutions will be required if success in reversing the population-wide weight increases that have occurred over the past several decades is to be achieved.

Key Words: *Diabetes; Lifestyle modification; Metabolic syndrome; Obesity; Prevention*

La prévention des maladies cardiovasculaires : L'obésité, le diabète et le syndrome métabolique

On prévoit que la pandémie actuelle d'obésité provoquera une morbidité et une mortalité en aval, de même que des coûts incrémentiels dans les systèmes de santé des quatre coins du monde. On s'attend que les principales complications métaboliques de l'obésité (le diabète de type 2 et le syndrome métabolique) soient particulièrement coûteuses. De récents essais aléatoires et contrôlés ont démontré que des interventions sur le mode de vie qui assurent de modestes pertes de poids réussissent à retarder ou à prévenir l'apparition du diabète de type 2 chez les personnes à haut risque. Cependant, sur le plan pratique, les stratégies de prévention de l'obésité et les programmes « dans le monde réel » ont démontré l'efficacité limitée de perdre du poids. Il est probable que ce à quoi on peut s'attendre de mieux avec les stratégies préventives actuelles, largement axées sur les changements de comportement, demeure la prévention d'une prise de poids supplémentaire. Jusqu'à récemment, les facteurs environnementaux, sociaux, psychologiques et économiques de l'épidémie d'obésité ont été sous-estimés et sous-accentués comme éléments contributifs à la pandémie. Les futurs efforts devront porter sur ces facteurs et il faudra adopter des solutions pansociétales pour réussir à renverser la prise de poids observée depuis quelques décennies dans l'ensemble de la population.

DIABETES, OBESITY AND THE METABOLIC SYNDROME: THE SCOPE OF THE PROBLEM

The global prevalence of obesity and overweight has markedly increased over the past several decades in both developed and developing nations. Currently, approximately 1.6 billion people worldwide are overweight (defined as a body mass index [BMI] of 25.0 kg/m^2 to 29.9 kg/m^2) and 400 million are obese (BMI of 30 kg/m^2 or greater) (1). In Canada, approximately 60% of the adult population and nearly 25% of children and adolescents are either obese or overweight (2). Excess body weight leads to considerable morbidity, premature mortality, impaired quality of life and accounts for 2% to 8% of all health care costs in developed nations (3,4).

Of the many health conditions associated with obesity, the cardiometabolic sequelae are among the most prevalent and can arguably be considered to be the most deadly. Compared with individuals who have a normal BMI, the 10-year risk of developing diabetes is increased approximately 20-fold in persons with a BMI of 35 kg/m^2 or greater (5). Type 2 diabetes increases the risk of myocardial infarction and stroke by at least two- to threefold, and approximately doubles the risk of all-cause mortality (6). It is also the leading cause of end-stage renal disease, blindness and nontraumatic amputations in developed countries (7). In addition, excess body fat – particularly visceral adiposity – predisposes toward the metabolic syndrome, which is characterized by dysglycemia, hypertension, dyslipidemia and a proinflammatory, prothrombotic state (8). A meta-analysis of 21 studies (9) demonstrated that the metabolic syndrome is associated with an increase in the risk of death from cardiovascular disease (RR 1.4; 95% CI 1.2 to 1.6) and overall mortality (RR 1.7; 95% CI 1.3 to 2.4).

Because these processes are often slow to evolve, the current pandemic of obesity and overweight is predicted to lead to a marked increase in diabetes and metabolic syndrome prevalence in the coming decades. Between 1999 and 2002, the prevalence of the metabolic syndrome in the United States was 35% (10), which represents a 59% increase over the period between 1988 and 1994 (11). Currently, 5.9% (nearly 250 million individuals) of the population worldwide has diabetes – a figure that is expected to increase to 380 million (7.1% of the population) by 2025 (12).

DIABETES PREVENTION IN HIGH-RISK PATIENTS IS FEASIBLE

Recent randomized controlled trials have demonstrated that prevention or delay of type 2 diabetes is feasible in high-risk populations. A meta-analysis of eight studies (13) involving 4573 patients reported that lifestyle modification reduced the incidence of type 2 diabetes in patients at risk for type 2 diabetes by 63% (95% CI 49% to 79%). In the United States, it is estimated that 19% of the population has prediabetes and would be considered at high risk for progression to type 2 diabetes (14).

The largest of these trials was the Diabetes Prevention Program (DPP) (15), a four-year (mean follow-up 2.8 years) randomized controlled trial involving 3234 individuals with prediabetes. Patients were randomly assigned to placebo, metformin or intensive lifestyle modification. The lifestyle modification intervention involved a 16-session core curriculum delivered by a multidisciplinary team over 24 weeks, which was followed by a long-term maintenance program. Weight losses of 7%, dietary fat intake reductions to less than 25% of total

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calories, an overall caloric intake of 1200 kcal/day to 1800 kcal/day and at least 150 min of physical activity per week were recommended. Weight losses of 0.1 kg in the placebo group, 2.6 kg in the metformin group and 5.6 kg in the lifestyle modification group were achieved. Compared with placebo, the incidence of type 2 diabetes was reduced by 56% (from 11% to 4.8%; 95% CI 48% to 66%) with intensive lifestyle modification and by 29% (from 11% to 7.8%; 95% CI 17% to 43%) with metformin therapy. The three-year cost effectiveness of the intervention as it was delivered in the DPP was $50,000 USD/quality-adjusted life year (QALY) and $27,000/QALY in modified form (primarily assuming that the intervention would be given in groups of 10 rather than on an individual basis) (16). Long-term (30-year) cost effectiveness for the lifestyle intervention varied between $8800/QALY to $63,000/QALY depending on the type of economic model used and the underlying assumptions regarding downstream complication rates (17).

These data demonstrate the feasibility of reducing the incidence of diabetes in high-risk individuals using lifestyle modification. However, the cost-effectiveness estimates vary widely and it is unclear as to how the DPP intervention or similar interventions will be delivered within current health care systems. Therefore, how to translate these important findings into 'real world' settings remains unclear (18).

OBESITY PREVENTION STRATEGIES HAVE DEMONSTRATED LIMITED EFFECTIVENESS

While studies such as the DPP have proven the efficacy of preventing diabetes in high-risk groups, what of the effectiveness of diabetes prevention in similar individuals or even the wider population-at-large? The three major strategies that have been examined include school-based programs, workplace programs and population-based educational programs.

Because children spend a substantial portion of their lives in a structured school environment, school-based interventions have received a great deal of attention as a means to halt current trends in childhood overweight and obesity. A systematic review (19) of 38 trials examining interventions to prevent childhood obesity found that one of three diet studies, five of 15 physical activity studies, and nine of 20 combined diet and physical activity studies, reported significant and positive differences between intervention and control groups with respect to BMI. In the studies that demonstrated significantly positive results, the magnitude of the BMI or weight change was marginal. Although the uptake of healthy behaviours is increasing, these results suggest that significant weight loss is demonstrated only in a minority of studies; hence, weight maintenance – not weight loss – is a more realistic expectation from such interventions.

Workplace programs have the potential to influence 65% of the population 16 years of age and older (20). Implementing successful weight-management programs at the workplace also has the potential to reduce obesity-related illnesses, injuries, absenteeism, disability and insurance claims. A systematic review (21) of nine randomized controlled trials evaluating workplace intervention programs that used multicomponent interventions (diet, exercise and behavioural modification) reported a modest weight reduction of 1.3 kg (95% CI 0.4 kg to 2.1 kg) compared with controls.

A systematic review (22) of adult obesity prevention studies examined randomized controlled trials with highly variable sample sizes (n=40 to approximately n=50,000) and length of follow-up (three to 90 months). Educational and behavioural modification techniques that involved dietary modification, exercise or both led to statistically significant control group-subtracted weight losses in only four of 11 studies. Furthermore, the studies reporting significantly positive results demonstrated modest weight differences between intervention and control groups of 0.4 kg to 3 kg. These differences were primarily due to weight increases in the control groups over time as opposed to weight reductions in the intervention groups.

Similarly, nonrandomized population-based obesity programs that used preventive strategies based largely on education alone appear minimally effective at reducing body weight (23). Other potential intervention strategies that are being proposed or are currently under early stage investigation include such measures as modifying the built environment to encourage healthier lifestyles, changes in food policy (eg, subsidies for foods deemed healthier; taxation of less healthy choices such as sweetened beverages; nutrition labelling; and banning of food advertising to children) and limiting children's screen time.

PANSOCIETAL UPTAKE IS REQUIRED TO DRAMATICALLY REDUCE OBESITY PREVALENCE

The rapid rise in obesity prevalence over the past several decades is clearly a consequence of our predisposition toward efficient fat storage coupled with the sedentary, calorie-laden environment in which we live. Indeed, on a population-wide level, widespread food shortages secondary to war or economic crises are the only 'interventions' that have dramatically reduced the prevalence of obesity and cardiovascular disease in modern times. A notable example occurred in Cuba in 1989 when the collapse of the Soviet Union resulted in the loss of economic aid and precipitated a nationwide economic crisis (24). During this time, food and fuel shortages led to a reduction in the per capita daily energy intake from 2899 kcal/day to 1863 kcal/day, and a rise in the prevalence of physical activity to nearly 70%. This resulted in a dramatic reduction in the prevalence of obesity (from 14% to 7%) and was associated with a decrease in deaths attributed to diabetes by 51%, coronary heart disease by 35%, stroke by 20% and all causes of death by 18%. The fact that the estimated daily energy intake of Cubans during that particular economic crisis was still higher than the upper limit of recommended energy intake for individuals enrolled in the DPP trial suggests that the degree of energy restriction advised in the latter trial is impractical to achieve in times of food abundance.

Although not an example of a 'voluntary' obesity prevention program, the Cuban experience clearly illustrates the scope of intervention that will be required to dramatically shift population-wide health behaviours and reduce the prevalence of obesity and downstream complications. A recent intervention program in France demonstrated that a dramatic, pansocietal uptake of an intervention program is, indeed, voluntarily feasible. The Fleurbaix-Laventie Ville Sante (FLVS) study (25) performed repeated cross-sectional surveys of obesity prevalence in school-age children (five to 12 years) in the northern French towns of Fleurbaix and Laventie following a five-year period (1992 to 1997) of nutritional intervention in schools. The intervention was implemented by teachers who received instruction from dieticians that included nutritional education, cafeteria modification, visits to local farms and cooking classes. Although this phase of the study was primarily intended to be a school-based intervention, rapid uptake within the community occurred from 1999 onward, and included significant media exposure, involvement of local decision makers and businesses. Dieticians and exercise therapists were employed, sports complexes were built and walking days were organized. Compared with neighbouring towns that served as controls, the prevalence of obesity in school-age children in the intervention towns in 2004 was 48% lower (8.8% versus 17.8%; $P<0.0001$). A larger scale intervention based on the FLVS study approach is currently being implemented across France, Spain and Belgium under the acronym EPODE (*Ensemble, Prévenons l'Obésité Des Enfants* [Together Let's Prevent Childhood Obesity]).

ADDITIONAL FACTORS THAT MUST BE ADDRESSED

Additional – often underappreciated – potential contributors to increased adiposity include psychosocial and socioeconomic factors such as mental illness, substance abuse, social inequity, social isolation, and sleep deprivation (Figure 1) (26-28). Although a causal role between these factors and obesity has not been established, it is likely that this undercurrent of psychosocial dysfunction is playing a significant role

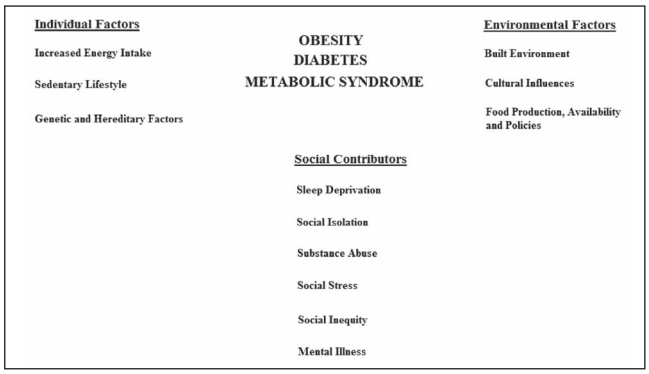

Figure 1) *Proposed factors contributing to the pandemics of obesity and related metabolic conditions*

in the rising prevalence of obesity and overweight. However, addressing these issues is a difficult task because they are ingrained into the very fabric of contemporary society, and the complex inter-relationships that likely exist have yet to be fully defined or appreciated. For example, several types of psychological dysfunction have been associated with obesity including binge eating, emotional eating, night eating, anxiety, sexual or emotional abuse, attention deficit disorder, depression and anxiety (26). In many cases, drug treatments for these disorders can exacerbate weight gain and lead to overt type 2 diabetes and the metabolic syndrome (29). In other cases, successful treatment of obesity and dramatic weight loss can produce a resurfacing of latent psychosocial pathology and sabotage further therapeutic success (26).

CONCLUSIONS

Historically, we have considered the emergence of the pandemics of obesity and related metabolic conditions to be largely the result of a mismatch of energy balance on an individual level and interventions have largely been focused at promoting individual change. While lifestyle modification to prevent diabetes and reduced weight in high-risk patients has clearly been efficacious in clinical trial settings, the translation of this evidence into real-world effectiveness has been difficult. Therefore, given the poor effectiveness of current strategies, a realistic goal on a population-wide level is to prevent a further rise in obesity prevalence. To produce a dramatic reduction in the prevalence of obesity, diabetes and the metabolic syndrome, a pansocietal uptake of interventions will be needed and measures to address related psychosocial and socioeconomic contributors will likely be necessary.

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