Prevention of Diabetes: Countless Opportunities and Clear Challenges

Abstract: *Prevention of diabetes poses significant challenges; especially when applied as public health intervention. While several trials, most importantly Diabetes Prevention Program, show that intensive lifestyle modification leading to weight loss is the most important intervention, many individuals and some populations may show resistance to these interventions. Roadblocks to lifestyle intervention alone or in combination include: age, some ethnic groups (e.g., south Asians), genetic make-up, and some characteristics of body phenotype. Recent data show that non-alcoholic fatty liver disease along with insulin resistance may constitute 'metabolically unhealthy phenotype'. These subgroups would need more intensive interventions to convert prediabetes to normal glucose regulation. Whether 'fatty pancreas' and sarcopenia, latter more often seen in Asian Indians and with advancing age, are other phenotypes requiring intensive and different interventions (e.g., more resistance exercise in latter) remains to be researched. Further, variations in dietary quality (Mediterranean diet enriched with extra virgin olive oil, high-protein diets) without changing much of calories, provide attractive options for*

intervention. Many of such innovations require more research. Translation of lessons from diabetes prevention studies to general population is daunting but possible. However, such community-based interventions need substantial human and material resources, which pose hurdles in underserved populations and developing countries. In such situations, low-cost modalities, for example, use of trained community educators and digital and social media, constitute attractive approaches.

Keywords: Community intervention; Deep abdominal adipose tissue; fatty liver disease; Non-alcoholic; Prediabetes; South Asians

number of patients and the huge burden of complications, rapid advances have been made in the treatment of diabetes. To stem this tide, the focus, however, should be to strengthen strategies and research for the prevention of diabetes. Prevention of diabetes poses significant challenges, especially when applied in public health mode. This task is more difficult in resource-constrained developing countries where diabetes is rapidly increasing.²

In this issue of the journal, Galaviz and colleagues have put together a comprehensive and evidence-based review on lifestyle-based modalities for the prevention of diabetes. These authors have, in simple and succinct manner,

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The relentless march of the diabetes epidemic continues throughout the world, particularly affecting low- and middle-income countries.¹ Commensurate with the increasing

explained the pathophysiology of diabetes and the effects of lifestyle interventions on reversal of prediabetes, and related metabolic factors. Several issues, some briefly discussed in this

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review, need to be stressed and discussed.

An often-discussed point is variations in occurrence and severity of insulin resistance and diabetes in different populations.³ For example, development of diabetes in South Asians is nearly a decade earlier than in other ethnic groups.⁴ In other words, the dysmetabolic state leading to diabetes occurs earlier in life in South Asians possibly starting in the first and second decades itself.⁵ It is interesting to note that South Asian children are more insulin resistant than white Europeans throughout childhood, even at 8 years of age.⁶ Others have argued whether poor nutrition before, during, and after pregnancy has a role in inducing early insulin resistance and dysglycemia in children born with low birth weight. Such a state of malnutrition *in utero* and after birth is largely seen in low- and middle-income countries, but it may be seen in people belonging to the low socioeconomic stratum living in developed countries as well. For example, black women belonging to the low socioeconomic stratum have twice the preterm birth rate and higher rates of growth restriction than do most other women in the United States.⁷ In this context, it is also important to note that African Americans are also more insulin resistant and have upregulated beta-cell functions as compared with non-Hispanic whites.⁸ One of the explanations of ethnic variations of insulin resistance and dysmetabolic state has been the “thrifty gene hypothesis” in these susceptible populations. Whether improvement of prenatal, perinatal and early infancy nutrition could avert insulin resistance and diabetes later in life remains a valid research question.

A narrow window of opportunity is available if conversion to diabetes from prediabetes is rapid, as is the case in some ethnic groups. Transition to diabetes from the state of prediabetes is more rapid in South Asians than Whites in the United Kingdom. Sattar and Gill in their elegant review show markedly different annual rates of conversion from prediabetes to diabetes in these ethnic groups: 12% to 18% in South Asians as

compared with 5% to 11% in white Europeans.⁹ These data emphasize the need for early and more aggressive intervention for diabetes prevention in South Asians. Furthermore, it is important to achieve normal glucose regulation (NGR) as early as possible after diagnosis of prediabetes. In the Diabetes Prevention Program Outcome Study, after 15 years of initial enrolment in the Diabetes Prevention Program (DPP) study, those individuals who achieved NGR, even if transient, significantly reduced risk of future diabetes independent of previous treatment, meaning achieving NGR was more important than the method to achieve it. Specifically, individuals who could achieve NGR status at least once during DPP had a 56% lower risk for incident diabetes versus those who consistently had prediabetes.¹⁰

An important observation in DPP study, as mentioned by Galaviz and colleagues, is that for every kilogram of weight loss, there was a 16% reduction, adjusted for changes in diet and activity, and overall 58% reduction in risk to conversion to diabetes with lifestyle-based interventions.¹¹ What is also encouraging to note in the same trial is that higher weight loss could lead to >90% reduction in risk for incident diabetes. Achievement of such weight loss is often difficult, transient, and thus frustrating to many, often resulting in loss of compliance. What are the factors that promote progression of prediabetes to diabetes despite aggressive lifestyle interventions in some individuals? This issue has been frequently debated and less researched. Variations in response to lifestyle or drugs (metformin) could be due to age, gender, genetics, ethnicity, or unknown factors. For example, in about 15% to 20% of individuals, body mass index (BMI), body fat, or insulin resistance do not improve even after an optimal exercise program (‘exercise resistance’). It is possible that heritability, DNA sequence variation, and/or epigenetic modifications may determine this failure of exercise response.¹² In this context, it is interesting to note that South Asians needed to undertake exercise 232 (95% confidence

interval = 200 to 268) minutes per week in order to obtain the same cardiometabolic risk factor score as a white European undertaking 150 minutes of moderate-equivalent physical activity per week.¹³ Further to that, as stated by Galaviz and colleagues, it is interesting to note differential effects of physical activity on types of prediabetes; lower progression to diabetes in individuals with isolated impaired glucose tolerance (primarily characterized by muscle insulin resistance) and inadequately successful to prevent progression to diabetes in individuals with isolated impaired fasting glucose (primarily characterized by hepatic insulin resistance).¹⁴ As the authors have rightly suggested, further innovations in lifestyle-based interventions are required for the prevention of isolated impaired fasting glucose.

Age is an important determinant for conversion from prediabetes to diabetes; in Finnish DPP, the intervention was most effective among the oldest individuals, with a relative risk reduction of 64% for diabetes as compared with that in the control group.¹⁵ Similarly, gender/gender-associated morbidity may modify response to lifestyle or drugs but needs more research. For example, in women with history of gestational diabetes, both metformin and lifestyle changes were effective in preventing diabetes, while metformin did not work in those without.¹⁶ In a systematic review of diabetes prevention studies (DPP translations from 2003 to 2012; total 17 studies) involving largely the African American population, much lower (by 50%) average weight loss was achieved than that seen in the DPP intervention.¹⁷ As is clear from the preceding discussion, more research is required regarding major roadblocks of interventions to prevent diabetes in women, different ethnic groups, and minority populations and those belonging to low socioeconomic status. At this point, it is important to recall that minority and underserved populations are at disproportionately high risk for diabetes in the United States.¹⁸

Another important factor for the varied response to lifestyle intervention could be the body phenotype of an individual. Most

diabetes prevention studies have categorized individuals by BMI. However, insulin resistance may vary in persons with similar body weight and BMI because of differential and varied deposition of adipose tissue and changes in skeletal muscle mass. In this respect, deposition of fat in truncal and abdominal regions is important and has been extensively researched.^{19,20} While Galaviz and colleagues have briefly discussed the role of intra-abdominal visceral adipose tissue and hepatic fat in the genesis of insulin resistance and diabetes, associations of specific abdominal adipose tissue depots and other 'ectopic fat' depots in relation to insulin resistance and prediabetes/diabetes need more discussion. Several studies show that truncal subcutaneous adipose tissue and intraabdominal adipose tissue affect insulin sensitivity.¹⁹ High-quality imaging protocols using magnetic resonance imaging has shown that further division of subcutaneous abdominal adipose tissue into superficial and deep locations.²¹ Posterior abdominal adipose tissue,²² appears to be distinct from the former anatomically and physiologically and may significantly contribute to insulin resistance,²¹ subclinical inflammation, and oxidative stress.²³ Of note, this deep subcutaneous abdominal adipose tissue increases with degree of obesity and is higher in South Asians as compared with whites.²⁴ Another interesting association is between sarcopenia (low skeletal muscle mass and function) with type 2 diabetes. An analysis of National Health and Nutrition Examination Survey III data show that sarcopenia is associated with adverse glucose metabolism and prediabetes independent of obesity, particularly in younger individuals, and that it could be an early marker of susceptibility to diabetes.²⁵ In this context, it is important to note that sarcopenia in South Asians, as compared with European whites and blacks, is more strongly associated with diabetes, independent of other factors.²⁶ Overall, it would be interesting to research the response of glycemia to lifestyle interventions in prediabetic individuals with excess deep abdominal adipose tissue or sarcopenia or both.

Increasing emphasis is being given to the relationship of hepatic fat (non-alcoholic fatty liver disease [NAFLD]) with insulin resistance and diabetes.²⁷ In a significant investigation, Seppala-Lindroos et al²⁸ looked at hepatic fat (measured with proton magnetic resonance spectroscopy), regional adiposity (intra-abdominal, subcutaneous abdominal, and total abdominal adipose tissue), and hepatic insulin sensitivity (measured using euglycemic, hyperinsulinemic clamp technique). In regression analyses, these authors showed that suppression of hepatic glucose output was significantly related to hepatic fat content independent of BMI and subcutaneous abdominal adipose tissue volume in normal men, showing the independent effect of hepatic fat on insulin sensitivity. An additional contributing factor for the pathogenesis of insulin resistance may be excess pancreatic fat (non-alcoholic fatty pancreatic disease) in individuals with prediabetes. Specifically, volume and fat content of pancreas is increased in persons with prediabetes and diabetes and has been shown to be correlated with insulin sensitivity.^{20,29,30}

Based on discussion by Galaviz and colleagues in their article and our previous discussion, it is clear that age, abdominal obesity, and both insulin resistance and insulin secretion play important roles in the development of prediabetes and in conversion of prediabetes to diabetes. Question remains regarding other factors that might impede regression of prediabetes to NGR. There is some evidence to show that presence of liver fat, along with other factors as mentioned above, may pose a roadblock to effective lifestyle interventions and may constitute a 'metabolically unhealthy phenotype.' Stefan et al³¹ investigated individuals with high-risk phenotype (low insulin sensitivity and presence of NAFLD) and a low-risk phenotype (all other traits) and showed that while both groups lost similar weight, only 31% of former (vs 67% in the latter) reverted to NGR. These data, though preliminary, are interesting enough to warrant further investigations.

Evidence is increasing that the genotype of an individual could determine accumulation of hepatic fat and insulin secretion. Interestingly, ethnic variations of hepatic steatosis have been seen in the United States; frequency was highest in Hispanics followed by whites and lowest in blacks linked to an allele in the *PNPLA3* gene.³² Thus, variation in *PNPLA3* contributes to ancestry-related and inter-individual differences in hepatic fat content and susceptibility to NAFLD, which, in turn, may determine insulin sensitivity. Furthermore, significant genetic influence on insulin secretion could be through the TT genotype at rs7903146 of *transcription factor 7-like 2 gene (TCF7L2)* gene, which could predispose to progression from prediabetes to diabetes,³³ as has been briefly mentioned by Galaviz and colleagues in their article. It is important to put more resources in this interesting field of research. The genotype-phenotype of an individual with prediabetes could be considered in determining appropriate intervention approaches of differing intensities.

Variations in dietary quality, without changing much of calories, provide an attractive option for intervention in individuals with prediabetes. In a study with 4.1 years median follow-up, among persons with high cardiovascular risk, a Mediterranean diet enriched with extra virgin olive oil but without energy restriction reduced diabetes risk.³⁴ Interestingly, if women adhered to the Mediterranean diets, incidence of gestational diabetes was shown to be lower than those who did not.³⁵ Another option is to increase the protein content in diets, which may increase satiety, improve insulin-glucose metabolism, and may preserve lean mass in individuals with sarcopenia. In a randomized controlled trial, we have recently shown that a high-protein meal (energy composition of test diet: 47% carbohydrate, 24% fat, and 29% protein) replacement strategy works well on metabolic factors of Asian Indians over 12 weeks; improvement was seen in weight, lipids, glycemia, insulin, and inflammatory markers.³⁶ Remarkably, in a

preliminary study on 24 women with prediabetes, a high-protein (30%) diet meal for 6 months reversed all individuals to NGR with improved insulin sensitivity as compared with a normal (15%) protein diet.³⁷ This dietary approach could be particularly useful for sarcopenic individuals with prediabetes and having normal renal functions.

Till now, discussion has suggested that lifestyle measures are effective in reversing prediabetes to NGR in most individuals. However, it is difficult to translate proven prevention strategies to the populations in an effective manner, particularly in resource-poor settings. Even in developed countries, prevention efforts have been suboptimal: poor risk factor assessment, underutilization of screening tests and counselling, and limited referral for glucose and lipid screening tests. In addition, structured behavioral recommendations for weight loss, physical exercise, and diet were inadequate.³⁸ It is important to note that such community-based interventions need considerable human and material resources. Furthermore, limited understanding of health issues (complicated by illiteracy in low-income communities in many countries), personal priorities different from health, and poor reach of healthcare workers in remote areas pose considerable roadblocks in underserved populations. Interestingly, interventions could be driven effectively by lay community educators also, as emphasized by Galaviz and colleagues in their article. Such a strategy may make more real-world and economic sense and may be suitable for developing countries with limited economic resources. In a recent study from India and Pakistan, multi-component care using non-physician care coordinators and decision-support electronic health records was effectively delivered to patients with diabetes with satisfactory results.³⁹ Another useful approach could be delivery of preventive and management advice at the doorsteps of people using customized diabetes care vehicles, though this mode needs more research.⁴⁰

New digital communication technologies show promise for delivering physical activity and diet interventions. These could be particularly attractive options for people

residing in developing countries where increasing use of smartphones is seen.⁴¹ With the use of text messaging, significant weight loss has been seen in individuals with prediabetes in the United States.⁴² Furthermore, trials done in China⁴³ and India⁴⁴ have also shown encouraging results. In particular, in the Indian study, the cumulative incidence of type 2 diabetes was significantly lower (18%) in the intervention group (received frequent lifestyle-related mobile phone messages) versus that in the control group (standard lifestyle modification advice at baseline only; 27%; hazard ratio = 0.64, 95% confidence interval = 0.45-0.92; $P = .015$).⁴⁴ While these methods are promising and appear to have considerable promise in the future, cost of smartphones, digital illiteracy in older individuals, and reluctance to embrace new technology by many, especially older persons, pose challenges.

To reiterate from my previous article, prevention of diabetes is a “long and winding road.”⁴⁵ A lot has been learned but weighty tasks remain. Effective translation of lessons learned from research and evidence to the ‘grassroots level’ of community constitutes the greatest challenge.

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Not applicable, because this article does not contain any studies with human or animal subjects.

Informed Consent

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Trial Registration

Not applicable, because this article does not contain any clinical trials. [AJLJM](#)

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