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PERSPECTIVE

Prevention of type 2 diabetes—success story that is waiting for next steps

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What is already known?

Type 2 diabetes can be prevented in people at high risk

The epidemic of type 2 diabetes (T2DM) has gained increasing attention already since 1980s. The burden of the disease is twofold due to multiple severe and costly chronic complications, in particular cardiovascular and microvascular diseases. Strategies for the prevention of T2DM have been proposed already over two decades [1, 2]. T2DM is one of the major chronic non-communicable diseases (NCDs) according to WHO (http://www.who.int/diabetes/global-report/en/) considered to be preventable by changing lifestyles and prevention of diabetes is an integral part of prevention of NCDs worldwide; the goal is to reduce mortality from diabetes by 25% and stopping the increase in prevalence of diabetes globally by 2025.

An important issue is that prevention of any disease should be based on solid scientific data. Fortunately, we have such evidence regarding T2DM prevention that we discuss in this brief review, emphasising that this evidence comes from proper prevention trials of T2DM with lifestyle intervention. In particular, we discuss key findings from the Finnish Diabetes Prevention Study (see summary Table 1) [3–19] that was the first individually randomised controlled trial proving that T2DM is preventable by enhanced multidomain lifestyle management [3].

Sustained reduction of the risk of type 2 diabetes can be maintained for many years after a lifestyle intervention programme

It is now unequivocally proven that in high-risk people T2DM is preventable or its onset can be postponed by multidomain lifestyle management comprising weight reduction, increasing physical activity and healthy dietary choices [19]. Long-term follow-up results obtained after the active prevention trial period from three major intervention trials carried out in China, Finland and the USA uniformly showed that lifestyle interventions applied during the trials have resulted in a sustained reduction in the incidence of T2DM lasting for several years after stopping the active intervention [4, 5, 20, 21]. In the DPS, the long-term risk reduction after 13 years of follow-up even increased by additional 37% during the post-intervention period [5]. In the Chinese Da Qing follow-up study risk reduction was 43% in the lifestyle intervention groups compared with no-intervention control clinics during the 20-year follow-up [20]. In the DPP, the corresponding risk reduction after 10 years of follow-up in the former lifestyle intervention group was 34% [21]. Overall, in these proof-of-concept landmark trials the diagnosis of T2DM was postponed with lifestyle intervention by ~5 years. As opposed to the "preventive" effect of glucose-lowering medications applied in some trials in prediabetes that disappeared after stopping medication, lifestyle changes seem to correct underlying pathophysiological mechanisms that lead to progression to overt T2DM in high-risk individuals [19].

Which factors explain the long-term T2DM risk reduction?

Long-term weight reduction is the cornerstone and main indicator in the prevention of T2DM and in keeping with our knowledge from observational studies about the main risk factors of T2DM [22]. It should be, however, kept in mind that body weight can only be reduced by decreased

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Table 1 Brief summary of selected main findings from the Finnish Diabetes Prevention study (DPS)

First author [reference]	Main findings	Comments
Tuomilehto [3]	58% reduction in the incidence of T2DM in intervention group	The first individually randomised trial to show that T2DM is preventable by multidomain lifestyle management
Lindström [4, 5]	Lifestyle intervention effect maintained over 10 years after the active intervention	Legacy effect possibly associated with long-lasting weight loss and improvement in insulin sensitivity and insulin secretion
Lindström [6]	Risk reduction of T2DM is associated with high fibre but relatively low-fat diet	The only diabetes prevention trial that reports dietary data in detail
Wikström [7] Lindström [8]	Educational attainment is not associated with the diabetes risk reduction. DPS intervention participants with a high estimated diabetes risk had the largest risk reduction.	Intervention works regardless of participants' educational background and seems to be particularly effective in people with a high diabetes risk
Uusitupa [9], de Mello [10]	Improvement in insulin sensitivity is strongly related to weight reduction, suggestive evidence that also preservation of the beta-cell function may contribute to the reduced risk of T2DM	Data based on repeated intravenous glucose tolerance test (IVGTT), and in particular long-term follow-up data on insulin sensitivity and insulin secretion indices
Herder [11, 12]	Diabetes risk is associated with low-grade inflammation, and among the lifestyle factors increasing physical activity and dietary fibre intake are associated with the decreased low-grade inflammation	Dietary fibre may be related to benefits on both insulin secretion and low-grade inflammation
Hämäläinen [13]	Lifestyle intervention, in particular weight loss, improves fibrinolysis	Based on repeated measurements of PAI-1
Uusitupa [14]	Lifestyle intervention seems to be effective independently of genetic or familiar risk of T2DM	People at high genetic risk benefit significantly from healthy lifestyle and can reduce their diabetes risk
Lindgren [15]	Lifestyle intervention is cost-saving for payers and cost-effective concerning high-risk people	Important issue to know among health providers
Uusitupa [16]	Lifestyle intervention seems to be associated with a low cardiovascular risk in people with IGT	Statistical power may not be sufficient in this regard, furthermore we found a particular low risk of CVD in both intervention and control groups
Tuomilehto [17]	Long sleep duration was associated with increased type 2 diabetes risk	Good sleep is, in addition to healthy diet and physical activity, the third lifestyle component for diabetes prevention
Penn [18]	Weight loss of 5% or more at year 1 leads to 65% lower diabetes risk during 3 year follow-up	Weight reduction is a useful surrogate for diabetes risk reduction

dietary energy intake and/or increased energy expenditure by physical activity. In the DPS, we have shown that a good compliance with major goals of lifestyle changes resulted in the greatest risk reduction [3, 5]. In the European Diabetes Prevention Study (EDIPS) combining the data of three European intervention trials, sustained weight reduction at least 5% for 3 years was associated with a particularly low risk of incident T2DM [18]. The Spanish PREDIMED trial used extra virgin olive oil with or without nuts added to the traditional Mediterranean diet showing a significant ~40% risk reduction in T2DM incidence [23]. The risk reduction in PREDIMED was be attributed to diet or some of its components, not to weight loss.

Physical activity was equally effective in preventing T2DM in people with impaired glucose tolerance (IGT) as was healthy diet in the Da Qing study [24]. In the DPS, after adjusting for weight changes and other confounding factors, we observed that increasing physical activity resulted in roughly 50% reduction in the risk of T2DM [25]. Thus, the increase in physical activity seemed operate independently of weight change. None of the T2DM intervention trials report post-intervention results related to the effects of physical activity alone. A recent systematic analysis concludes however that evidence on the effect of physical activity alone is insufficient for the prevention of T2DM [26].

What we are getting to know now?

Does lifestyle changes modify morbidity and mortality in individuals at high risk of T2DM?

Unfortunately, this important question cannot be properly answered, since the current evidence is only derived from post-hoc analyses from few trials not designed for morbidity/mortality outcomes. Many potential confounding effects that were not possible to control for, making inferences from findings on mortality and morbidity very difficult. Among various T2DM prevention trials five studies that have reported long-term morbidity and mortality data [16, 27–30] and confirmed that there was no concern about the safety issue with lifestyle interventions.

In the Da Qing 23-year follow-up study [28] both total mortality (HR 0,71) and cardiovascular mortality (HR 0,59) were lower in former intervention clinics than in the control clinics. Furthermore, severe retinopathy was 46% lower in intervention groups. The US DPP has not reported mortality or cardiovascular morbidity data, but the former lifestyle intervention group showed the lowest occurrence of microangiopathic complications among the three treatment arms (lifestyle 8.7%, vs. control 11.0% and metformin group 11.2%; $p = 0.03$) [29]. Furthermore, microvascular complications were 28% lower in individuals who survived without diabetes than in those who developed incident diabetes before the occurrence of microangiopathic complications. In the DPS [16] and Malmo Study [27] participants with IGT, had lower cardiovascular and total mortality than in people with IGT in the general population, but no differences were found between intervention and control groups. In PREDIMED the composite cardiovascular event rate was reduced by 30% in people using extra virgin olive oil [30].

Current dietary recommendations work

The trials where incidence of T2DM has been the main end point have applied diets with (moderately) reduced fat. Other common features have been, in accordance with the general recommendations, increased consumption of vegetables, fruit and whole grains. Using the DPS data of dietary intakes collected with food diaries we analysed in more detail the effect of diet on the incidence of T2DM; the lowest incidence of diabetes was found in study participants with high fibre and moderate fat intake [6]. Also, the dietary intervention used by the DPS intervention group was very similar to that applied in the US DPP [31] and EDIPS [18] trials. The recent comprehensive report "The evidence-based nutrition guidelines for the prevention and management of diabetes" from Diabetes UK recommends the main dietary approaches that were applied in the DPS trial (;[32] www.diabetes.org.uk/nutrition-guidelines).

Genetics, biomarkers and metabolites in relation to prevention of T2DM

Genetics of T2DM

The progress in the field of genetics of T2DM has advanced our knowledge of the disease markedly. Nevertheless, currently known genetic variants explain only a fraction of the heritability of T2DM and low frequency variants may not add much in this regard [33]. Studies on interaction between genetic factors and lifestyles are rare. Based on the DPS results we have analysed the interaction between genetic risk score (high vs. low) including 19 well-known risk SNPs and lifestyle on the incidence of T2DM. Lifestyle intervention effects seemed to overcome the genetic risk, and the same is true with respect to positive family history. The results remained about the same after adjustment for fasting and post-load glucose and insulin values at OGTT [14]. The findings from the US DPP have been in keeping with these results [34].

Inflammatory markers and biomarkers

Low-grade inflammation is typical finding in obesity, metabolic syndrome and T2DM [35]. Furthermore,

inflammation may play a role in adipose tissue dysfunction, fatty liver and beta-cell failure in long-run, all suggested to be linked to the pathophysiology of T2DM. In the DPS, we have shown that high hs-CRP in control and high RANTES concentrations in intervention group predicted T2DM after 1-year follow-up [12]. We have also shown lower values for hs-CRP and IL-6 in intervention group. Among the factors that associated with lower values of inflammatory markers were high dietary fibre intake and physical activity suggesting their fundamental role in improving glucose metabolism [11]. Different biomarkers may predict the development of T2DM. In the DPS markers of low absorption and high synthesis of cholesterol were associated with the risk of developing T2D in one of our studies [36]. A recent pooled analysis suggests that omega-6- fatty acids may be protective while omega-3 fatty acids had no significant association with the incidence of T2DM [37].

What we do we need to know in the future?

Interaction with genes and personalised medicine

Analyses on low frequency and rare genetic variants seem not offer much more in improving genetic heritability of T2DM. Age, physical inactivity and obesity are more powerful risk indicators of T2DM than genetic risk scores [38]. Nevertheless, the knowledge about genes is important when it comes to deeper understanding of pathophysiology of T2DM in various population groups. It will be possible to tailor drug treatment of T2DM according to the genetic background. As for prevention of T2DM, prospective studies are needed to explore the value of genetic testing in risk individuals. Trials need to be designed based on genetic risk profiling, since the current knowledge is sufficient to plan such T2DM prevention strategies [34, 38]. Prospective studies with sufficient power are needed to confirm the results from secondary analyses of previous trials [39].

The major prevention trials included people with prediabetes who had IGT, i.e. showed a high glucose excursion after a glucose load. Prediabetes may also be characterised by high fasting glucose, called impaired fasting glucose (IFG) that has been said to have different pathophysiology than IGT [40]. High fasting glucose indicates overproduction of glucose by liver during the night. It is possible that we need different kinds of interventions based on the pathophysiology behind different dysglycaemia phenotypes, since for instance the Japanese trial in people with IFG did not reveal any benefits in those with isolated fasting glucose elevation, but only in those who also had IGT [41] in keeping with results from other trials in people with IGT [3, 19, 25, 31].

Metabolomics

Metabolomics studies offer a new approach to study factors that may be involved in the pathogenesis of T2DM. Metabolites analysed from body fluids may reflect dietary intakes, metabolites originating from microflora of gastrointestinal tract or those formed in the body metabolism. Using metabolomics data it is possible to discover early biomarkers for T2DM (amino acids, ketones, etc.) [42]. In DPS participants several novel metabolites were associated with lower likelihood of developing T2D, including indole and lipid related metabolites. Indolepropionic acid originating from gut microbiota were associated with better insulin secretion and lesser low-grade inflammation modified by fibre intake, while several lipid metabolites, certain amino acids and bile acid metabolites were associated with insulin resistance [43].

Does “optimal diet” for diabetes prevention exist?

Different suggestions and opinions regarding different dietary approaches offered for the prevention of T2DM exist. Observational studies have been instrumental to point out associations between different dietary factors and incidence of T2DM. The recent systematic review including major food groups showed that T2DM was lower in people consuming whole grains, fruits and low-fat dairy products, and increased among those with high intakes of red meat, processed meat and sugar-sweetened beverages consumption [44, 45]. However, true long-term results are lacking from studies applying and comparing various dietary modifications in intervention settings. Studies on dietary biomarkers and metabolites may offer novel approach to examine the effects of quality of diet [43].

The Mediterranean diet is nowadays often suggested as the best diet to prevent chronic diseases including T2DM, and many components of the Mediterranean diet indeed are in line with the dietary goals of the T2DM prevention trials [32]. Although the Mediterranean diet is relatively high in fat, it seems that the quality of fat is more important than quantity regarding T2DM prevention. From weight loss trials we know that the best weight reduction diet is the diet a person can and is willing to follow, and therefore palatability and accessibility are important for the long-term compliance. Fortunately, a diet mainly based on vegetables, fruits, whole grains, and sources of vegetable proteins and oils is not only preventing T2DM, but also climate protecting. Various diet options have been offered for the prevention and treatment of T2DM. Any low-energy diet results in weight reduction, but long-term efficacy of for instance ultra-low energy, high protein and ketogenic diets still need to be proven for long-term safety and sustained weight reduction. Such diet has been used in management

of T2DM [46], and may be useful for some high-risk obese individuals to prevent progression to diabetes.

Cardiovascular outcomes

One can estimate the likely effect on cardiovascular disease events with data from observational studies, because each 1.1 mmol/L difference in fasting plasma glucose concentration is associated with a 20% difference in cardiovascular disease risk [47]. Thus the difference of 0.5 mmol/L or less seen in previous trials should lower risk by 8% or less. This means that the number needed to treat people with prediabetes for 3 years to prevent one cardiovascular disease event would be very high, more than 500, and for such a trial the total sample size needed would be ~20,000. However, as PREDIMED trial showed [30], an intervention that will have multiple beneficial effects may also reduce cardiovascular events.

Mobile health technology in T2DM prevention

Prevention of T2DM based on mobile health (mHealth) offers a feasible and cost-effective method for lifestyle intervention delivered via a mobile phone application along with the support of a health coach. In an Indian trial the incidence of T2DM was reduced from 27% in the control group to 18% in those who received mobile phone messages ($p = 0.015$). The number needed to treat to prevent one case of type 2 diabetes was 11 [48]. High levels of mobile phone ownership globally affords the potential to scale up effective mHealth interventions for delivery to large populations. If the results of this trial are replicated in other settings, this method may become a practical way to deliver lifestyle advice to prevent T2DM.

T2DM prevention in the real world

While the proof-of-concept trials have provided scientific basis for T2DM prevention in high-risk people [22], a substantial challenge remains in organising prevention services as a part of routine clinical practice. Interventions used in clinical trials, to ensure lifestyle change, need to be translated into interventions that are deliverable in real-world health care systems. Several countries have initiated plans and programmes for T2DM prevention with varying experiences [49, 50]. Effectiveness can be improved by maximising guideline adherence. Also, optimal strategies for maximising both cost-effectiveness and longer-term maintenance of healthy lifestyle and weight loss need to be tested. Another approach, the population strategy for T2DM prevention need to be developed together with other policies collaborating with the health sector. The population strategy must have a strong link with comprehensive national food and nutrition policies.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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