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REVIEW

Pathophysiology and aetiology of impaired fasting glycaemia and impaired glucose tolerance: does it matter for prevention and treatment of type 2 diabetes?

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Abstract Prior to the development of type 2 diabetes, glucose levels increase into the prediabetic states of isolated impaired fasting glycaemia (i-IFG), isolated impaired glucose tolerance (i-IGT), or combined IFG/IGT. A better understanding of the aetiology and pathophysiology of the prediabetic states might give a basis for the development of individualised prevention and treatment strategies for type 2 diabetes. Several studies have examined mechanisms and potential aetiological factors leading to the development of the different prediabetic states. The pathophysiology of i-IFG seems to include the following key defects: reduced hepatic insulin sensitivity, stationary beta cell dysfunction and/or chronic low beta cell mass, altered glucagon-like peptide-1 secretion and inappropriately elevated glucagon secretion. Conversely, the prediabetic state i-IGT is characterised by reduced peripheral insulin sensitivity, near-normal hepatic insulin sensitivity, progressive loss of beta cell function, reduced secretion of glucose-dependent insulinotropic polypeptide and inappropriately elevated glucagon secretion. Individuals developing combined IFG/IGT exhibit severe defects in both peripheral and hepatic insulin sensitivity as well as a progressive loss of beta cell function. The aetiologies of i-IFG and i-IGT also seem to differ, with i-IFG being predominantly related to genetic factors, smoking and male sex, while i-IGT is predominantly related to physical inactivity, unhealthy diet and short stature. Since the transition from the prediabetic states to overt type 2 diabetes is characterised by a non-reversible vicious cycle that includes severe deleterious effects on glucose metabolism, there are good reasons to use the well-established aetiological and pathophysiological differences in i-IFG, i-IGT and IFG/IGT to design individualised preventive strategies.

Keywords Beta cell dysfunction · Environmental factors · Genetic factors · Impaired fasting glycaemia · Impaired glucose tolerance · Insulin resistance · Pathophysiology · Prevention · Review · Treatment

Abbreviations

2hPG	2 h plasma glucose
EGP	Endogenous glucose production
FPG	Fasting plasma glucose
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
IFG/IGT	Combined impaired fasting glycaemia and impaired glucose tolerance
i-IFG	Isolated impaired fasting glycaemia
i-IGT	Isolated impaired glucose tolerance
NGT	Normal glucose tolerance

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Introduction

The key hormonal defects responsible for hyperglycaemia in type 2 diabetes are decreased insulin secretion [1] and elevated glucagon secretion [2, 3], but also the secretion

and action of the gut incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are altered in type 2 diabetes [4]. These defects contribute to elevated endogenous glucose production (EGP) from the liver [5] and kidney [6], which in combination with peripheral (muscle) insulin resistance [1] lead to hyperglycaemia. In addition, adipose tissue affects glucose metabolism through altered release of adipocytokines [7] and NEFAs into the bloodstream [8]. Also hypothalamic insulin signalling affects regulation of EGP and hepatic insulin resistance in rodents [9], underscoring the concept of type 2 diabetes as a multiple organ disease [10].

Prior to the development of type 2 diabetes, glucose levels increase into the prediabetic states of isolated impaired fasting glycaemia (i-IFG), isolated impaired glucose tolerance (i-IGT), or combined IFG/IGT. The predominant metabolic abnormality of the specific prediabetic state is likely to track into the development of type 2 diabetes, giving rise to different type 2 diabetes phenotypes with potentially different requirements for prevention and treatment. A better understanding of the aetiology and pathophysiology of the prediabetic states might give a basis for the development of individualised prevention and treatment strategies for type 2 diabetes. This article reviews mechanisms and potential aetiological factors leading to the development of the prediabetic states i-IFG, i-IGT and IFG/IGT, and ultimately to type 2 diabetes. Furthermore, the article addresses the possibility of using this pathophysiological and aetiological knowledge in optimising individualised prevention and treatment of type 2 diabetes.

Pathophysiology of i-IFG, i-IGT and IFG/IGT

Muscle

Peripheral insulin sensitivity is important for lowering blood glucose levels after an OGTT, since most of the glucose in this period is taken up by skeletal muscle [11]. Conversely, in the fasting state, approximately 50% of glucose uptake occurs in the insulin-insensitive brain tissue, while mainly fatty acid oxidation is responsible for energy expenditure in muscle tissue [12]. Therefore, insulin sensitivity in muscle tissue will not markedly influence plasma glucose levels in the fasting state. Studies using euglycaemic–hyperinsulinaemic clamp techniques in prediabetic individuals have supported this. They found that peripheral insulin sensitivity is decreased in individuals with i-IGT, while it is normal in those with i-IFG [13–18] (Fig. 1a).

In large epidemiological studies where insulin sensitivity has been estimated by use of glucose and insulin levels measured during an OGTT, we and others also found reduced insulin sensitivity in individuals with i-IFG [19–21] (Fig. 2a). The discrepancy between the findings from the clamp and the OGTT studies is likely to be caused by the fact that the liver plays a larger role during the OGTT than during the clamp. During a euglycaemic–hyperinsulinaemic clamp, EGP is almost fully suppressed [22], and clamp-derived estimates of insulin sensitivity therefore primarily reflect insulin action in skeletal muscle. Conversely, during oral glucose ingestion, insulin levels are lower [13] and EGP is less suppressed [12]. Accordingly, estimates of insulin sensitivity derived from post-OGTT levels of glucose and insulin may reflect both hepatic and peripheral insulin action. In support of this, a study [23] recently demonstrated that hepatic insulin sensitivity accounted for one-third, whereas peripheral insulin sensitivity accounted for two-thirds of glucose disposal after a meal in healthy individuals.

Liver

Elevated EGP from the liver, caused by increased gluconeogenesis [24], is a hallmark of type 2 diabetes. In individuals with i-IFG, the absolute level of EGP does not appear to be elevated [13, 14, 25]. However, two studies [14, 25] found elevated basal insulin levels in individuals with i-IFG, and they suggested that EGP was disproportionately elevated. This indicates that hepatic insulin resistance is a key defect in i-IFG. We were not able to demonstrate hepatic insulin resistance in individuals with i-IFG when studied by use of tracer technique [13]. A likely explanation is that our study participants had progressed from normal glucose tolerance (NGT) to i-IFG within 5 years, and therefore they did not yet have significantly elevated fasting insulin levels. However, we found that HOMA index of insulin sensitivity, predominantly reflecting hepatic insulin sensitivity, was decreased in individuals with early detected i-IFG [19] (Fig. 2b). Individuals with i-IGT do not have elevated EGP or hepatic insulin resistance [13, 14], which is most probably related to their normal fasting glucose levels.

Pancreas

Insulin secretion Several studies have demonstrated decreased insulin secretion (as indicative of beta cell dysfunction) in prediabetic individuals with i-IFG [13–15] (Fig. 1b). Recently, we showed that individuals who progressed from NGT to i-IFG within 5 years were characterised by a constitutive, stationary defective beta cell function or chronic reduced beta cell mass [26], which was already present before fasting hyperglycaemia was demonstrated [19] (Fig. 2c,d). Continued beta cell apoptosis

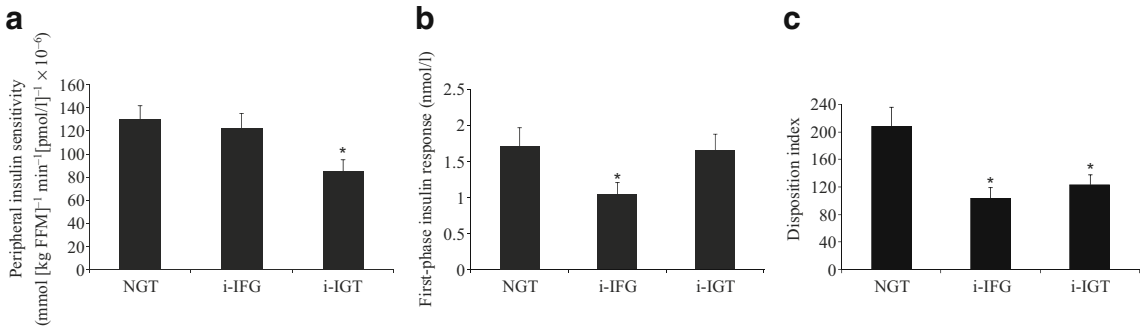

Fig. 1 **a** Peripheral insulin sensitivity (mean+SE) during a euglycaemic–hyperinsulinaemic clamp; **b** first-phase insulin response (geometric mean+SE) during an IVGTT; and **c** disposition index (first-phase insulin response×peripheral insulin sensitivity; geometric mean±SE, arbitrary unit) in 20 individuals with NGT, 18 with i-IFG and 28 with i-IGT. *p<0.05 vs NGT and i-IFG (**a**); *p<0.05 vs NGT and i-IGT (**b**); *p<0.05 vs NGT (**c**). Adapted from Færch et al. [13]. FFM, fat-free mass

is not likely to cause the defective beta cell function, since this would lead to a progressive and not a stationary loss of beta cell function. However, if individuals with i-IFG develop peripheral insulin resistance, beta cell function or mass may progressively decline in these individuals in the same manner as in individuals with i-IGT [19], IFG/IGT [19, 27] and type 2 diabetes [1, 28].

A major determinant for regulation of beta cell mass and function is glucose concentration [29]. In the early states of impaired glucose regulation, pancreatic beta cells adapt to insulin resistance (i.e. increased blood glucose levels) by increasing mass and function [29]. However, by calculating the disposition index, we and others [13, 19, 30, 31] could not find evidence of an appropriate compensatory increase in insulin secretion in individuals progressing from NGT to i-IFG or i-IGT (Fig. 1c). Only individuals progressing from NGT to IFG/IGT seem to exhibit a compensatory increase in insulin secretion [19, 32] (Fig. 2c). This could indicate that more severe abnormalities in both the fasting and the postprandial states may be necessary for increasing the insulin-secretory capacity of pancreatic beta cells. However, it should be noted that a short-term compensatory increase in insulin secretion may be followed by exhaustion with time.

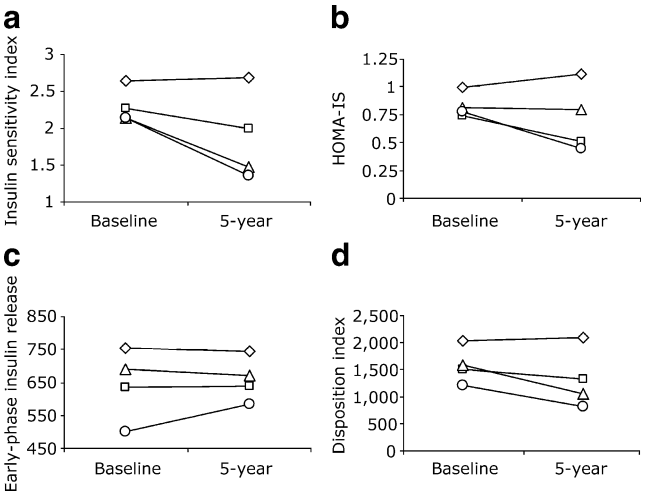

Fig. 2 **a** Insulin sensitivity index; **b** HOMA-insulin sensitivity (HOMA-IS); **c** early-phase insulin release and **d** disposition index of beta cell function in individuals with NGT at baseline who maintained NGT status (n=2,842, diamonds) or who progressed to i-IFG (n=83, squares), i-IGT (n=192, triangles) or IFG/IGT (n=28, circles) within 5 years. Data are medians (arbitrary units). p<0.05 for differences in 5-year changes: i-IGT vs NGT, IFG/IGT vs NGT (**a**); i-IFG vs NGT, IFG/IGT vs NGT, i-IGT vs i-IFG, IFG/IGT vs i-IGT (**b**); i-IGT vs NGT (**c**); i-IGT vs NGT, IFG/IGT vs NGT, i-IGT vs i-IFG (**d**). Adapted from Færch et al. [19]

Glucagon secretion Glucagon acts as a counter-regulatory hormone to insulin and may therefore play an essential role in type 2 diabetes pathophysiology. Many patients with type 2 diabetes have increased alpha cell mass [33], which contributes to disproportionately elevated fasting glucagon levels [2, 3]. Whether these alterations in glucagon secretion are secondary to other metabolic defects in type 2 diabetes or whether they are primary to the disease is not fully understood.

Only few studies have examined glucagon secretion in individuals with impaired glucose regulation. Two studies [34, 35] found near-normal fasting and post-OGTT glucagon levels in individuals with IGT (i-IGT and IFG/IGT together). However, when glucagon concentration was related to the ambient levels of insulin or glucose, they found a reduced suppression of glucagon secretion [34, 35]. Two other studies [36, 37] demonstrated elevated glucagon levels in both obese and non-obese IGT individuals, and we also previously reported that both individuals with i-IFG and individuals with i-IGT had significantly elevated fasting and post-OGTT glucagon concentrations compared with individuals with NGT [13]. Overall, these findings in individuals with impaired glucose regulation indicate that abnormal pancreatic alpha cell function may be a signifi-

cant and early abnormality in the pathogenesis of type 2 diabetes. However, since glucagon levels are increased in both individuals with i-IFG and individuals with i-IGT, the different pathogenesis of fasting vs postprandial glucose regulation may not be explained by differences in glucagon secretion.

Gut

Few studies have published data on incretin hormone secretion in individuals with i-IFG and i-IGT [13, 32]. We previously reported that individuals with i-IFG may compensate for a reduced beta cell function by increasing the secretion of GLP-1 [13]. This finding was contrasted by the European Network on Functional Genomics of Type 2 Diabetes (EUGENE2) study [32], which found reduced secretion of GLP-1 during an OGTT in individuals with i-IFG. In the EUGENE2 study [32], first-phase insulin response was not impaired in individuals with i-IFG, which might explain why GLP-1 secretion was not compensatingly elevated [13]. Also, the fact that the EUGENE2 study [32] was a multicentre study with a very heterogeneous population might have contributed to the different findings. GIP levels were normal in i-IFG individuals in our study [13] and in the EUGENE2 study [32].

Individuals with i-IGT seem to be characterised by a reduced secretion of GIP during OGTTs [13]. Studies in individuals with IGT (i-IGT and IFG/IGT together) also showed partial impaired incretin effect [38, 39] as well as reduced GIP [40] and GLP-1 secretion [41].

Despite observed alterations in gut incretin hormone secretion in individuals with NGT and prediabetes [13, 32, 38, 39, 41], the current thought is that the reduced incretin hormone secretion and action observed in type 2 diabetes is likely to be secondary to other hormonal and metabolic alterations, such as hyperglucagonaemia [42]. Prospective observational studies in individuals progressing from NGT to type 2 diabetes are needed to establish the natural history of incretin hormones in the development of type 2 diabetes.

Adipose tissue

Adipose tissue is an active endocrine organ, secreting several products into the bloodstream, of which adipokines (e.g. leptin, adiponectin, resistin and visfatin) and cytokines (e.g. TNF-α, IL-1 and IL-6) are involved in obesity-related insulin resistance and inflammation [7]. In patients with type 2 diabetes, basal NEFA levels are often increased [5], lipolysis in adipose tissue is not adequately inhibited by insulin [8] and lipid oxidation is increased [24]. Only a single study has examined the role of the adipose tissue in the prediabetic states i-IFG and i-IGT [43]. It found that both individuals with i-IFG and individuals with i-IGT had increased resistance to the lipolytic action of insulin in the adipocytes. However, individuals with i-IFG seemed to be able to compensate for this adipocyte insulin resistance by increasing their basal insulin secretion, thereby keeping NEFA levels in the normal range. In contrast, those with i-IGT had elevated NEFA levels, indicating an enhanced rate of lipolysis despite normal basal insulin levels [43]. More studies are needed to confirm these findings, but also the role of adipocytokines in the development of i-IFG and i-IGT deserves attention in future studies.

Brain and kidney

Both brain and kidney may play important roles in type 2 diabetes pathophysiology [10], but no studies have yet examined the function of these organs in relation to the development of the different prediabetic conditions.

Summary

The pathophysiological characteristics of i-IFG, i-IGT and IFG/IGT are summarised in Table 1.

Aetiology of i-IFG, i-IGT and IFG/IGT

Environmental factors

Environmental factors play an enormous role in type 2 diabetes aetiology. However, only few studies have examined the individual and isolated roles of common environmental risk factors in the development of fasting and postprandial hyperglycaemia (i-IFG and i-IGT).

Physical inactivity The effect of physical inactivity on glucose metabolism predominantly includes impairments of peripheral insulin-stimulated glucose uptake (i.e. peripheral insulin resistance) [44, 45]. The findings that physical activity is associated with 2 h plasma glucose (2hPG) levels and i-IGT, but not with fasting plasma glucose (FPG) levels and i-IFG [19, 46–48] support this notion.

Diet In addition to physical activity, diet plays a central role in type 2 diabetes aetiology. In particular, the total dietary fat amount and intake of saturated fat increase the risk of developing impaired glucose regulation and type 2 diabetes [49, 50], while high intakes of dietary fibre and wholegrain products decrease the risk [51]. Since we do not eat single dietary components, but mixed meals, analyses of dietary patterns [52] or dietary scores [53] have attracted much attention during recent years. Recently, we found that the dietary quality of individuals who developed i-IGT was lower than that of those who developed i-IFG and IFG/IGT

Table 1 Pathophysiology of the prediabetic states

Pathophysiology	i-IFG	i-IGT	IFG/IGT
Muscle			
Insulin sensitivity	Unaltered	Reduced	Reduced
Liver			
Insulin sensitivity	Reduced	Unaltered	Reduced
Hepatic glucose production	Elevated	Unaltered	Elevated
Pancreas			
First-phase insulin response	Reduced	Reduced or unaltered	Reduced
Disposition index[a]	Reduced	Reduced	Reduced
Glucagon secretion	Elevated	Elevated	Elevated
Gut			
GLP-1 secretion	Reduced or elevated	Reduced or unaltered	?
GIP secretion	Unaltered	Reduced or unaltered	?
Adipose tissue			
Insulin sensitivity	Reduced	Reduced	?
NEFA release	Unaltered	Elevated	?
Adipocytokine release	?	?	?
Brain	?	?	?
Kidney	?	?	?

[a] Disposition index is the first-phase insulin response adjusted for peripheral insulin resistance

?, Not studied

[19]. Moreover, in the Inter99 study a dietary pattern consisting of high intakes of, for example, high-fat meats, mayonnaise, potatoes and butter predicted an increase in 2hPG levels, but not in FPG levels at 5 years of follow-up [54]. In addition, the Hoorn study [55] and the Finnish and Dutch cohorts of the Seven Countries Study [49] found associations between dietary factors and 2hPG levels, but they did not examine the relationship between diet and FPG levels. Together these findings support the idea that diet predominantly affects mechanisms associated with peripheral insulin action, for instance modification of membrane phospholipids [56].

Smoking Smoking increases the risk of type 2 diabetes in both men and women [57]. We recently found that smoking was associated with elevated FPG levels in men but not in women, whereas 2hPG levels were not affected by smoking [46]. In contrast, smoking was associated with elevated 2hPG levels in men in the Hoorn study [55]. The effect of smoking on glucose metabolism may be mediated through a modification of body composition [58], but smoking may also cause long-lasting and chronic impairments of both insulin secretion and insulin sensitivity, for instance because of damage caused by reactive oxygen species [59]. In addition, smoking may affect lipid metabolism. For instance, a significant relationship between smoking and hepatic lipase activity (fatty acid release from the liver) has been found [60]. This may be related to the hepatic insulin resistance observed in i-IFG individuals [14, 25].

Heritability

Although environmental factors are important determinants for type 2 diabetes, genetic components may be necessary for the disease to develop. Recently, we found that a family history of diabetes was associated with elevated FPG levels, but not 2hPG levels [19, 46]. Several genes may contribute to this effect of family history of diabetes. In the following, we will discuss potential candidates.

The strongest association with type 2 diabetes has been observed for variants in the gene encoding transcription factor 7 like-2 (*TCF7L2*) [61]. Suggested mechanisms include impaired insulin secretion, blunted incretin effects, hepatic insulin resistance, enhanced rate of EGP and elevated FPG levels [62, 63], all features associated with the development of i-IFG and IFG/IGT. However, variants in *TCF7L2* have also been associated with elevated 2hPG levels [63], which makes it difficult to use variants in this gene to discriminate between individuals developing i-IFG and i-IGT.

Other genes with potential influence on fasting glucose regulation are *MTNR1B* [64–66], *GCK* [67, 68], *GCKR* [69, 70] and *G6PC2* [71–73]. These risk variants seem to have cumulative effects on FPG levels [66] (Fig. 3). In addition to being associated with FPG levels, the G allele of *MTNR1B* rs10830963 also increases the odds of having i-IFG and IFG/IGT but not i-IGT [64]. This variant may therefore be interesting with respect to identifying individuals who are at increased risk of developing isolated defects in fasting glucose regulation.

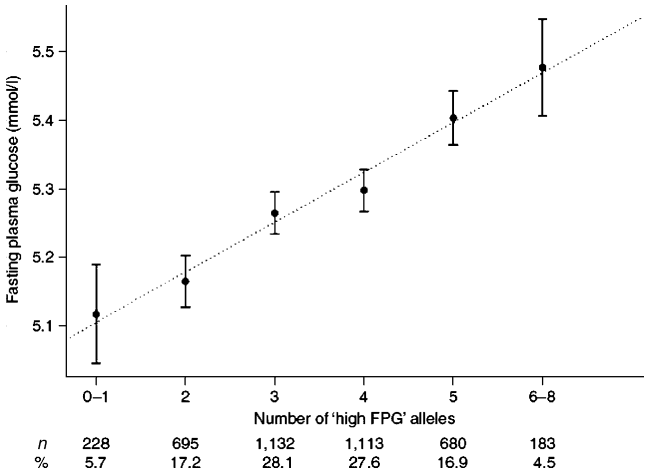

Fig. 3 Cumulative effects of *MTNR1B* rs1387153, *G6PC2* rs560887, *GCKR* rs1260326 (P446L) and *GCK* rs1799884 (–30G) variants on FPG levels in the Data from an Epidemiological Study on the Insulin Resistance syndrome (DESIR) study. Data are means (95% CI). The β coefficient (β=0.07, 95% CI 0.06–0.08, adjusted for age, sex and BMI, $p = 8 \times 10^{-33}$) corresponds to the increase in FPG levels by additional 'high FPG' alleles. Adapted with permission from Bouatia-Naji et al. [66]

No gene variants have been exclusively associated with 2hPG levels or i-IGT, but variants in *PPARG* and *FTO* have been associated with insulin sensitivity [74, 75], a key defect of i-IGT. However, since *PPARG* variants are not related to 2hPG levels [75, 76], and *FTO* variants are associated with elevated FPG levels and hepatic insulin resistance [77], neither of these gene variants is likely to be involved in the development of i-IGT.

Recently, a Danish group showed that it is not possible to effectively discriminate between individuals with NGT and type 2 diabetes by combining the effects of 19 validated type 2 diabetes gene variants [78]. Thus, it is still too early to make individualised prevention of type 2 diabetes based on genetic information.

Sex and anthropometry

Inverse relationships between height and 2hPG levels have been demonstrated in both men and women [46, 79], indicating that short individuals are more likely to be diagnosed with i-IGT than with i-IFG. Low birthweight is strongly related to short adult stature [80] as well as to the development of IGT and type 2 diabetes later in life [81–83]. Significant associations between low birthweight and adult FPG levels have also been demonstrated [84, 85], which indicates that low birthweight affects several pathways involved in glucose regulation. Whether low birthweight is more closely related to the development of i-IGT than to the development of i-IFG is not yet clear.

It is well recognised that the risk of developing type 2 diabetes is higher in men than in women [86, 87]. In addition, the prevalence of i-IFG is highest in men, whereas the prevalence of i-IGT is highest in women [17, 19, 79, 88]. Compared with men, women have higher postprandial and post-OGTT levels of plasma glucose, insulin, GIP and GLP-1 [41, 88, 89]. Differences in the ability to dispose of the ingested 75 g glucose because of differences in height and thereby muscle mass between men and women could explain the sex differences in the prevalence of i-IGT, as suggested by Sicree et al. [79]. Likewise, differences in metabolically active muscle mass between short and tall individuals exposed to the same amount of glucose may also partly explain the effect of height on 2hPG levels. Future studies using different amounts of glucose during OGTTs in men and women with different body composition might bring us closer to an understanding of the link between sex, anthropometry and 2hPG levels.

Summary

The aetiological factors associated with elevated fasting and/or 2hPG levels are summarised in Table 2.

Implications for prevention and treatment of type 2 diabetes

Prevention

When type 2 diabetes has become manifest, it is most often too late to reverse the glucotoxic effects of hyperglycaemia on beta cell function. Interventions to delay or even prevent the development of type 2 diabetes therefore seem more important than treatment, regarding population health and the burden of healthcare costs.

Since individuals with i-IFG and i-IGT are characterised by different pathophysiological features, the optimal prevention of type 2 diabetes may differ between these groups of individuals. For instance, it is not likely that lifestyle interventions mainly targeting peripheral insulin sensitivity are as equally effective in individuals with i-IFG as in those with i-IGT [90, 91]. Randomised follow-up studies with different intervention strategies (e.g. lifestyle intervention, metformin, incretin-based therapy and placebo) in high-risk individuals with i-IFG and i-IGT are needed to clarify whether alternative approaches may improve prevention of type 2 diabetes in those with i-IFG.

The findings that different risk factors may cause elevated plasma glucose levels in men and women [46] and that individuals who develop i-IFG and IFG/IGT are more likely to have a family history of type 2 diabetes [19] may be used in relation to risk assessment in the clinic. If other studies confirm these observations, new sex-specific

Table 2 Effects of aetiological factors on FPG levels (the development of i-IFG), 2hPG levels (the development of i-IGT) and combined FPG/2hPG levels (the development of IFG/IGT)

Aetiology	FPG levels (i-IFG)	2hPG levels (i-IGT)	FPG/2hPG levels (IFG/IGT)
Environmental factors			
Physical inactivity	No effect	Increase	?
Low dietary quality	No effect	Increase	No effect
Smoking	Increase	No effect or increase	Increase
Heritability			
Family history of diabetes	Increase	No effect	Increase
TCF7L2	Increase	Increase	?
MTNR1B	Increase	No effect	?
GCK	Increase	Increase	?
GCKR	Increase	No effect	?
G6PC2	Increase	No effect	?
FTO	Increase	No effect	?
PPARG	Increase	No effect	?
Sex and anthropometry			
Male sex	Increase	Decrease	No effect
Low birthweight	Increase	Increase	?
Short adult stature	No effect	Increase	?

?, Not studied

screening algorithms could be developed to improve prediction and prevention of type 2 diabetes.

Treatment

To clarify the pathophysiology of different type 2 diabetes phenotypes, there is a need for prospective studies in individuals developing diabetes dominated by defects in fasting glucose regulation vs defects in postprandial glucose regulation. Based on the current studies of individuals with i-IFG and i-IGT, it is likely that patients with isolated defects in fasting glucose regulation may benefit from medication targeting hepatic insulin sensitivity and beta cell function, whereas those with predominantly defects in 2hPG levels may benefit from medication or lifestyle changes targeting peripheral insulin sensitivity.

IFG and IGT as diagnostic criteria

About 10 years ago, the new definition of i-IFG gave rise to an increased focus on the pathophysiological differences between i-IFG and i-IGT, but recently it has been widely debated whether the use of i-IFG, i-IGT and IFG/IGT as diagnostic criteria should be reconsidered [92–94]. One of the major reasons is that the prediabetic states are likely to be continuums of impaired glucose regulation rather than being binary states. Furthermore, the definitions of i-IFG, i-IGT and IFG/IGT are based on rather arbitrary cut-off points from OGTTs with limited reproducibility [95]. However, even though the diagnostic criteria for diabetes and impaired glucose regulation may be changed, it is still important to bear in mind that individuals with elevated fasting glucose levels differ in aetiology and pathophysiology from those with elevated postprandial glucose levels and therefore may require different prevention and treatment.

Conclusions

In conclusion, the pathophysiology of i-IFG seem to include the following key defects: reduced hepatic insulin sensitivity, stationary beta cell dysfunction and/or chronic low beta cell mass, altered GLP-1 secretion and inappropriately elevated glucagon secretion. Conversely, the prediabetic state i-IGT is characterised by reduced peripheral insulin sensitivity, near-normal hepatic insulin sensitivity, progressive loss of beta cell function, reduced secretion of GIP and inappropriately elevated glucagon secretion. Individuals developing IFG/IGT exhibit severe defects in both peripheral and hepatic insulin sensitivity, as well as a progressive loss of beta cell function.

The aetiologies of i-IFG and i-IGT also seem to differ, with i-IFG being predominantly related to genetic factors, smoking and male sex, while i-IGT is predominantly related to physical inactivity, unhealthy diet and abnormalities associated with short adult stature. Aetiological factors associated with IFG/IGT have not yet been examined.

Since the transition from the prediabetic states to overt type 2 diabetes is characterised by a non-reversible vicious cycle that includes severe deleterious effects on glucose metabolism, there are good reasons to use the well-established aetiological and pathophysiological differences in i-IFG and i-IGT to design individualised preventive strategies.

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