Review Article

Progression to and Prevention of Diabetes: Disparity of Impaired Fasting Glucose and Impaired Glucose Tolerance - Review Article

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It is well established that individuals who have prediabetes either impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) have high risk to develop diabetes. However, it is unclear whether the rate of progression to diabetes is different between these two categories. Lifestyle modification has been recommended for diabetes prevention in these high-risk groups. However, given the differences in their pathophysiology, it is possible that these subtypes of prediabetes condition may have different responses to lifestyle modification. The present review was to summarize the risk of progression to diabetes and the effectiveness of lifestyle intervention for diabetes prevention in individuals who have isolated IGT or isolated IFG or combined.

The risk of progression to diabetes is highest in combined IFG and IGT subtype. Individuals who have isolated IFG by the American Diabetes Association criteria (100 to 125 mg/dl) has lower risk of progression to diabetes than those with World Health Organization criteria (110 to 125 mg/dl) and the latter has similar or higher risk of incident diabetes than those with isolated IGT. Lifestyle modification is most effective in individuals with IGT (with or without IFG) but is less effective in those with isolated IFG.

In conclusion, The risk of progression to diabetes and the effectiveness of lifestyle intervention for diabetes prevention are disparate between prediabetes subtypes. Given the paucity of diabetes prevention data in individuals with isolated IFG, more studies dedicated to this subtype is required.

Keywords: Impaired fasting glucose, Impaired glucose tolerance, Prediabetes, Type 2 diabetes, Lifestyle intervention, Diabetes prevention

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Prediabetes is the condition of which glucose levels do not meet the criteria for diabetes but are too high to be considered normal. Individuals with prediabetes have increased risk of progression to diabetes compared with those without. Prediabetes is defined by the presence of impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). However, the definitions of IFG and IGT are somewhat different between organizations[1,2]. The studies of the risk of progression from IGT to diabetes are numerous, however, almost all those studies are performed in individuals with IGT with or without IFG. The studies dedicated to those with isolated IFG are relatively few. Only three studies were included in a meta-analysis previously reported by Gerstein et al[3]. Likewise, lifestyle intervention has been shown to be effective in reduction of incidence of type 2 diabetes in individuals who have IGT with or without IFG[4-7], it is uncertain whether this intervention is similarly effective in those who have isolated IFG. The recommended strategies of diabetes prevention at present do not discriminate between subtypes of prediabetes. Given the differences in pathophysiology of isolated IFG and isolated IGT as summarized in

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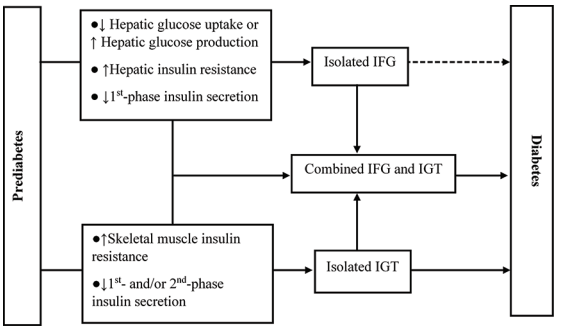

Figure 1. Pathophysiology of prediabetes subtypes and their progression to diabetes.

IFG=impaired fasting glucose; IGT=impaired glucose tolerance

Dotted arrow denotes less common path

Figure 1[8-13], it is plausible that the risk of progression to diabetes as well as the effectiveness of diabetes prevention strategies are disparate between these two prediabetes categories.

The purpose of the present review was to summarize the latest evidences from English language literatures about the risk of progression to diabetes and the effectiveness of lifestyle intervention for diabetes prevention in individuals with different subtypes of prediabetes (isolated IFG, isolated IGT, and combined IFG and IGT).

Risk of progression to diabetes in individuals with isolated IFG, isolated IGT, or combined IFG and IGT

The incidence of progression from prediabetes subtypes to diabetes in population-based long-term, follow-up studies is shown in Table 1[14-22]. Although there is a heterogeneity between studies, it appears that individuals with isolated IFG or isolated IGT have 3- to 7-fold higher risk of progression to diabetes compared with normal population and have much lower risk than those with combined IFG and IGT. This risk is lower in individuals with IFG as defined by the American Diabetes Association (ADA) than those as defined by the World Health Organization (WHO)[1,2]. Data from the Brazilian Longitudinal Study of Adult Health study in 15,105 Brazilian participants aged 35 to 74 years indicated that individuals who had isolated IFG by WHO definition had two folds higher risk of incidence of diabetes than those with ADA definition after 3.7 years of follow-up[22]. As shown in Table 1, it should be noted that, within the same cohort, individuals with isolated IFG by WHO definition have similar or greater risk of progression to diabetes than those with isolated IGT[14-18,22] whereas this risk is lower in those with isolated IFG by ADA definition[19]. Data from the 10-year prospective cohort study of the Atherosclerosis Risk in Communities Study indicated that individuals with prediabetes using WHO fasting glucose definition had higher positive predictive value and higher likelihood ratio of incident diabetes than those using ADA fasting glucose definition and those with IGT[23]. This is consistent with the previous meta-analysis by Gerstein et al[3], Morris et al[24], and recent systemic review by Richter et al[25].

The studies of the progression from isolated IFG or isolated IGT to diabetes are relatively few. The prospective cohort study by Meigs et al[26] in US adults indicated that 37% of 30 individuals who initially developed isolated IFG subsequently developed IGT whereas only 15% of the 225 initially developed isolated IGT subsequently developed IFG during ~11 years of follow-up. The progression to diabetes rarely occurred with isolated high fasting plasma glucose (PG) (126 mg/dl or more) but was more common with the combination of elevated 2-hour PG (200 mg/dl or more). These findings support the previous studies by Chou et al[27] in Chinese population and Shaw et al[28] in the Mauritius population. The progressive decline in beta cell function or worsening of insulin sensitivity may explain these observation[29]. However, it should be kept in mind that a significant number of individuals with isolated IFG, isolated IGT, or both, do not develop diabetes and 20% to 40% of those particularly obese individuals who can lose weight reverts to normal fasting or 2-hour PG levels with long-term follow-up[18,30-32].

No clinical characteristics can clearly distinguish individuals who will progress to isolated IFG or isolated IGT. However, it is noted that individuals with isolated IFG tend to be men or younger age whereas those with isolated IGT tend to be women or older age[13,26,29,33,34]. The Thai National Health Examination Survey IV study also supports this observation[35]. Likewise, the study in 6,884 high risk Thai population by Aekplakorn et al[36] indicated that women, individuals without family history of diabetes, and those with history of hypertension had higher prevalence of isolated IGT. Why women have higher prevalence of IGT than men is unclear. The smaller skeletal muscle mass in women has been shown to contribute to this gender disparity independent of insulin resistance and beta cell function[37,38]. Visceral fat is similarly increased in individuals with isolated IFG or isolated IGT, but hepatic fat content is significantly greater only in

Table 1. Incidence of progression from prediabetes to diabetes according to subtypes of prediabetes in population-based, long-term follow-up studies

Ethnic (reference)	Age (year)*	Prediabetes subtype (n)	FU (years)	Rate/1,000 patient-year (95% CI)	% cumulative incidence (95% CI)
Pima Indian, U.S.[14]	No data	Normal (4,269)	5	-	3.6
		IGT+IFGWHO (904)		-	41.2
		i-IGT (753)		-	19.9
		i-IFGWHO (251)		-	31.0
Dutch[15]	60.3±6.9	Normal (1,125)	6.4	7.0	4.5
		IGT+IFGWHO (31)		112.2	64.5
		i-IGT (80)		57.9	33.8
		i-IFGWHO (106)		51.4	33.0
Chinese, Taiwan[16]	48.9±12.5	Normal (435)	5	18.8	7.69
	58.9±11.9	IGT+IFGWHO (49)		112.0	42.21
	56.1±13.1	i-IGT (118)		60.7	22.31
	48.4±9.7	i-IFGWHO (42)		93.7	39.96
Iranian[17]	42.0±13	Normal (3,216)	6	-	2.9 (2.4 to 3.6)
		IGT+IFGWHO (77)		-	59.7 (47.9 to 70.8)
		i-IGT (442)		-	19.2 (15.7 to 23.2)
		i-IFGWHO (60)		-	20.0 (10.8 to 32.3)
Southern German[18]	62.7±5.4	Normal (463)	10.2	5.8 (3.9 to 8.3)	-
	63.8±4.8	IGT+IFGWHO (51)		76.0 (51.3 to 108.5)	-
	65.6±5.4	i-IGT (63)		35.2 (21.8 to 53.8)	-
	63.1±4.9	i-IFGWHO (75)		47.4 (32.8 to 66.2)	-
Chinese[19]	56.9±9.2	Normal (30,291)	3.8		2.9
		IGT+IFGADA (3,983)			12.7
		i-IGT (4,970)			8.8
		i-IFGADA (9,138)			5.0
South Korean[20]	59.1±10.1	IGT+IFGADA (119)	3.8	-	31.9
	63.0±11.0	i-IGT (65)		-	18.5
	60.2±11.3	i-IFGADA (158)		-	15.2
South Korean[21]	51.7±8.8	Normal (5,986)	10	14.7	-
		IGT+IFGADA (128)		86.0	-
		i-IGT (1,378)		56.9	-
		i-IFGADA (162)		43.8	-
Brazilian[22]	50.9 (50.8 to 51.1)	IGT+IFGADA (1,493)	3.7	-	25.5 (23.3 to 27.7)
		IGT+IFGWHO (531)		-	36.4 (32.3 to 40.4)
		i-IGT (2,245)		-	20.5 (18.8 to 22.1)
		i-IFGADA (4,870)		-	12.7 (11.8 to 13.7)
		i-IFGWHO (1,140)		-	25.4 (22.8 to 27.9)

ADA=American Diabetes Association; WHO=World Health Organization; Normal=normal fasting and 2-hour plasma glucose levels by ADA or WHO definitions; FU=follow-up; IFGWHO=impaired fasting glucose by WHO definition (fasting glucose 110 to 125 mg/dl); IFGADA=impaired fasting glucose by ADA definition (fasting glucose 100 to 125 mg/dl); IGT=impaired glucose tolerance; i-IFG=isolated impaired fasting glucose; i-IGT=isolated impaired glucose tolerance; SD=standard deviation; CI=confidence interval

* Age is expressed as mean±SD or 95% CI

those with isolated IGT[39-41].

From the available evidences, the risk of progression from prediabetes to diabetes is highest in individuals with combined IGT and IFG. This risk may be higher in isolated IFG than isolated IGT if the lower cut-off level of 110 mg/dl is used as IFG

Table 2. Effect of lifestyle intervention on the incidence of type 2 diabetes in individuals who have isolated impaired fasting glucose or isolated impaired glucose tolerance or combined impaired glucose tolerance and impaired fasting glucose in randomized controlled clinical trials

Ethnic (reference)	Age (year)+	Prediabetes subtype (n)	FU (year)	Rate/100 patient-year		Risk reduction (95% CI)
				Control	Lifestyle intervention	
Japanese[42]	49 (41 to 54)	IGT+IFGADA (262)	3	12.6	6.8	0.59 (0.31 to 0.76)
		i-IFGADA (379)		1.8	2.4	–0.17 (–1.74 to 0.5)
Indian[43]	44.4±9.3	IGT+IFGADA (232)	3	22.2	14.5	0.36 (0.03 to 0.57)
		i-IGT (172)		10.7	7.4	0.31 (–0.31 to 0.64)
		i-IFGADA (174)		7.2	6.5	0.12 (–0.57 to 0.80)
Indian[44]	46.0±7.5	IGT+IFGADA (116)	2	ND	ND	0.34 (0.02 to 0.55)
		i-IFGADA (227)		ND	ND	0.05 (–0.33 to 0.32)
U.S. (DPP)[6]	50.6±10.7	IGT+IFGWHO (1,060)	2.8	22.3	8.8	0.63 (0.51 to 0.72)
		i-IGT (2,174)		6.4	2.9	0.55 (0.38 to 0.68)
				Cumulative incidence (%)		
				Control	Lifestyle intervention	
Indian[45]	46.0±5.8	IGT+IFGWHO (178)	3	65.4	45.2	-
	45.5±6.0	i-IGT (667)		51.5	29.5*	-

DPP=diabetes prevention program study; FU=follow-up; IFGWHO=impaired fasting glucose by WHO definition (fasting glucose 110 to 125 mg/dl); IFGADA=impaired fasting glucose by ADA definition (fasting glucose 100 to 125 mg/dl); IGT=impaired glucose tolerance; i-IFG=isolated impaired fasting glucose; i-IGT=isolated impaired glucose tolerance; ND=no data; SD=standard deviation; CI=confidence interval

* $p<0.0001$ compared with IGT+IFG group, + Age is expressed as mean±SD or median (interquartile range)

definition. Substantially more individuals either with isolated IFG or isolated IGT progress to diabetes by a progressive increase of 2-hour PG levels.

Effectiveness of lifestyle intervention for diabetes prevention in individuals with isolated IFG, isolated IGT, or combined IFG and IGT

Lifestyle intervention has been shown to effectively reduce the incidence of type 2 diabetes in individuals with prediabetes in several populations[4-7]. However, all those studies included individuals with IGT, some of which also had IFG. Therefore, it is unclear whether lifestyle intervention would be as effective in those who have isolated IFG. There are only five studies that specifically answer this query (Table 2). Saito et al[42] recruited 641 obese Japanese with IFG to study the efficacy of lifestyle modification in prevention of diabetes, 262 of which also had IGT. They reported that after three years of study, lifestyle modification significantly reduced risk of type 2 diabetes only in those with combined IFG and IGT but not in those with isolated IFG. Weber et al[43] studied 578 overweight or obese Asian Indians who had isolated IFG, isolated IGT or combined IFG and IGT, and found that lifestyle intervention was most effective for diabetes prevention in individuals who had combined IFG and IGT, followed by those with isolated IGT. Diabetes risk reduction was minimal in individuals with isolated IFG and was not significantly different from the control group. Likewise, Thankappan et al[44] studied the effect of a 2-year peer-supported lifestyle changes for diabetes prevention in 1,007 high risk Indian population in Indian communities and found that the risk reduction was observed only in individuals with IGT (with or without IFG) but not in those with isolated IFG.

Table 2 demonstrates that the risk reduction with lifestyle intervention was substantially higher in individuals with isolated IGT or combined IGT and IFG than those with isolated IFG[6,42-45]. This risk reduction can be maintained for more than a decade in those who adhere to lifestyle changes[46-48]. It should be noted that the effect of lifestyle intervention on fasting and 2-hour PG levels is disparate between subtypes of prediabetes. Data from the Finnish Diabetes Prevention Program demonstrated that lifestyle intervention could improve the 2-hour PG in individuals with IGT either isolated IGT or combined IGT and IFG but not in those with isolated IFG[49]. Likewise, it could improve fasting PG in those with IFG either isolated IFG or combined IFG and IGT but not in those with isolated IGT. Data

from the US Diabetes Prevention Program indicated that IGT was more likely to be regressed in male subjects, individuals with lower baseline 2-hour PG and those with greater insulin sensitivity and IFG was more likely to be regressed in female subjects, individuals with lower baseline fasting PG, those with greater insulin secretion, greater weight loss, and use of metformin[50]. These findings support the respective roles of insulin resistance and defective insulin secretion in the pathogenesis of IGT and IFG as shown in Figure 1.

Why individuals with IFG or IGT respond differently to lifestyle intervention is intriguing. Lifestyle intervention that include weight reduction, caloric restriction, and regular exercise has been shown to improve peripheral insulin resistance and beta cell function[51-53], therefore, those with either IFG or IGT who adhere to the intervention should be responsive. It is plausible that the diet and exercise components of the intervention program may have differential effects on insulin sensitivity and beta cell function and may contribute to this discrepancy. Data from the Whitehall II and the Inter 99 studies, independently indicated that the leisure-time physical activity was associated with the reduction of 2-hour but not fasting PG and it did not predict progression to diabetes in individuals with isolated IFG[54,55]. This is supported by the recent study indicating that habitual daily physical activity was not associated with the improvement of beta cell function in individuals with IGT[56]. Slentz et al[57] studied the effect of varying degree of exercise amount or intensity and the effect of clinical lifestyle intervention (low amount and moderate intensity exercise combined with diet to reduce body weight for 7%) in 237 prediabetes subjects and reported that, after seven months, only clinical lifestyle intervention group experienced significant reduction in fasting PG. Exercise only had no effect on fasting PG despite the improvement in insulin sensitivity and slight decrease in body weight. It is possible that the substantial weight reduction by clinical lifestyle intervention is needed to improve fasting PG of individuals with IFG by reducing hepatic insulin resistance. It is unclear whether if clinical lifestyle intervention could be maintained for years, it could effectively prevent incident diabetes in isolated IFG subgroup.

These data indicate that different strategies may be required to prevent progression from IGT or IFG to diabetes. Regular increase in exercise or physical activity as suggested in several diabetes prevention programs may be adequate to delay or prevent the progression from IGT to diabetes. However, physical activity or exercise without significant weight reduction will have little impact on diabetes prevention in individuals with IFG. In fact, sustained weight reduction is the key element of the successful long-term diabetes prevention programs[58]. Since weight regain is very common in lifestyle intervention studies, this may be one of the reasons why lifestyle modification is less effective in individuals with isolated IFG.

Conclusion

The risk of progression to and the benefits of lifestyle modification in prevention of diabetes are disparate between individuals with IFG and those with IGT. The risk of progression to diabetes is highest in combined IFG and IGT subtype. Individuals with isolated IFG by WHO definition (110 to 125 mg/dl) has higher risk of progression to diabetes than those with ADA definition (100 to 125 mg/dl) and they may also have higher risk of incidence of diabetes than those with isolated IGT. In terms of diabetes prevention, lifestyle modification is most effective in individuals with IGT (with or without IFG) but less effective in those with isolated IFG. Given the paucity of diabetes prevention data in individuals with isolated IFG, more studies dedicated to this subtype is required.

What is already known on this topic?

Subjects with prediabetes, which include IFG and IGT, have high risk to progress to diabetes. Behavioral lifestyle modification is recommended in those subjects to prevent or delay type 2 diabetes. However, the risk of progression to diabetes and the effectiveness of diabetes prevention strategies may be different between these two subtypes.

What this study adds?

The risk of progression to diabetes and the effectiveness of lifestyle intervention for diabetes prevention are disparate between subjects with IFG and IGT. Different strategies for diabetes prevention may be required.

Conflicts of interest

The authors declare no conflict of interest.

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