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Rapid Deterioration of Insulin Secretion in Obese Adolescents Preceding the Onset of Type 2 Diabetes

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Abstract

Objective—To identify pathophysiologic changes that lead to the onset of type 2 diabetes (T2DM) in adolescents.

Study design—Obese adolescents with NGT (n=41) were studied longitudinally over 4 years with serial measure of the acute insulin response to IV glucose (AIR_g) as well as proinsulin (PI) concentrations. Insulin resistance was estimated with HOMA modeling, the disposition index (DI) computed as AIR_g × 1/HOMA-IR, and IV glucose tolerance estimated as the glucose disappearance constant (k_g).

Results—Four adolescents developed diabetes during the study (DM), and the rest of the cohort remained non-diabetic (NDM). Baseline PI exceeded the interquartile range of the NDM group in 3 of 4 subjects with DM and all had > 85% reduction from baseline AIR_g, and DI, within 6 months of diagnosis. All the subjects with DM gained weight over the course of the study but these changes paralleled those for the NDM group. HOMA-IR increased substantially in 1 of the subjects with DM at the time of diagnosis, but was comparable with baseline in the other 3. The DI and k_g of the subjects with DM was below the 10th percentile of the NDM group before and after diagnosis.

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Conclusion—Conversion from NGT to T2DM in adolescents can occur rapidly, and T2DM onset is heralded by a substantial decline in AIR_g and DI, as well as increased release of PI. These results support loss of beta-cell function as the proximate step in the development of T2DM in this age group.

Keywords

Disposition Index; HOMA-IR; acute insulin response; proinsulin

Type 2 diabetes (T2DM) has become an increasingly common problem in young people over the past two decades (1, 2). The rising prevalence of what had previously been thought of as a disease of adults has accompanied the general increase in obesity among children and adolescents. Similar to adults with T2DM, affected youth seem to progress through a prediabetic state marked by insulin resistance and impaired insulin secretion (3). In fact, the inability of islet β -cells to compensate for insulin resistance appears to be a core pathogenic mechanism underlying diabetes in patients of all ages (2, 4, 5).

The development of T2DM in adults is a progressive process that manifests over years and perhaps decades (6-8). Cross sectional studies in adults have demonstrated that at progressive levels of increased fasting glucose, or impaired oral glucose tolerance, β -cell function is decreased (9), and future risk of diabetes can be predicted well before any clinical manifestations arise (10, 11). Similar findings have been collected in adolescents showing differences in insulin resistance and insulin secretion across stages from normal glucose tolerance to prediabetes (3, 12, 13). Although it is clear that adolescents who develop T2DM are obese and insulin resistant, and also have abnormalities in beta-cell function, the pathophysiology behind the transition from prediabetes to diabetes is not well understood. Moreover, there is only limited information available about the pace of progression in young people, which is presumably more rapid than in adults to account for the development of clinical disease over the short period of adolescence (2). Although much more common than in the past, the incidence of T2DM in adolescents is still sufficiently low that prospective studies to identify pathophysiologic changes leading to disease have been impractical. In this paper we describe the development of T2DM in 4 adolescents over the course of a 4 year longitudinal study of insulin secretion in obesity. Our goal was to identify the key changes involved in the transition from normal glucose tolerance to diabetes, and our results support a rapid decline in β -cell function as the key feature in this progression.

Methods

The study population consisted of 41 obese adolescents with normal glucose tolerance (NGT) who comprised a control population for a longitudinal study of beta-cell function in adolescents with T2DM. Inclusion criteria consisted of onset of puberty (Tanner II breast development for girls, 4ml testicular volume for boys), a BMI greater than the 99th percentile for age and sex, and a normal 75g oral glucose tolerance test (OGTT) within 3 months of study initiation. Individuals were excluded if they had active concurrent illnesses, secondary diabetes or were pregnant. Five of the subjects who did not develop diabetes (nondiabetic, NDM), and one who eventually developed diabetes (diabetic subject 2, DM2),

were taking metformin as treatment for insulin resistance at the time of their entry into the study; control subjects taking metformin were excluded from the analysis, and the subject who developed DM was included. Over the course of observation 4 subjects developed type 2 diabetes (T2DM), leaving 32 adolescents in the NDM group at the conclusion of the 4 year study. Subject with DM2 continued on metformin after she was diagnosed and a second subject, DM1, was started metformin after diabetes diagnosis. Prior to enrollment, written informed consent/assent was obtained from all subjects or their parents (for those < 18 years old) according to the guidelines of the Cincinnati Children's Hospital and the University Of Cincinnati College Of Medicine Institutional Review Boards.

After an overnight fast subjects were admitted to the Clinical and Translational Research Center (CTRC) at the Cincinnati Children's Hospital Medical Center. Body weight was measured with a digital scale to the nearest 0.1 kg, and height was measured with a wall-mounted stadiometer to the 0.1 cm at each visit. Indwelling venous catheters were placed in both forearms for infusion of test substances and blood sampling. The arm designated for blood drawing was wrapped in a heating pad to maintain stable blood flow. Subjects received an intravenous bolus of dextrose (0.3 grams/kg, maximum dose 40 grams) and blood was sampled at 2, 4, 6, 8, 10, 12, 15, 18, 21, 25 and 30 minutes thereafter. Blood samples were immediately placed on ice and centrifuged to separate plasma within an hour of collection. Plasma was stored at -80°C until processing. After the initial visit, subjects returned at 6 months, 1, 2, 3, and 4 years.

Glucose measurements were made at the time of study on whole blood samples using a YSI glucose analyzer (Yellow Springs Instrument, Yellow Springs, OH). Plasma insulin was measured by radioimmunoassay (RIA) as previously described (14). This assay uses a guinea pig anti-insulin serum that does not distinguish between proinsulin and fully processed insulin. Proinsulin was measured using a commercial RIA kit (Millipore/Linco, Inc., St. Louis, MO). Hemoglobin A_{1c} (HbA_{1c}) was determined using a modification of a high-performance-liquid-chromatography method with an Alliance 2690/2695 HPLC (Waters Corporation, Milford, MA) and a PolyCAT A column (PolyLC, Inc Columbia, MD), and results reported as percent of total hemoglobin.

Statistical Analyses

Fasting glucose and insulin levels were calculated as the mean of two samples taken before glucose administration. Glucose disappearance during the IVGTT was estimated as the glucose disappearance constant (k_g) by calculating the slope of the $\ln[\text{glucose}]$ from 10-30 minutes. The acute insulin response to glucose (AIR_g) was computed as the area under the curve over baseline of insulin concentrations at 2, 4, 6, 8, and 10 minutes after IV glucose using Riemann sums based on the midpoint of each interval. Fasting proinsulin to insulin ratios (PI/I) were calculated for each subject before the glucose bolus by dividing the mean of two proinsulin measurements by the mean of two insulin measurements. Stimulated PI/I ratios were calculated using the mean PI value and mean of insulin value from +4 min and +10 min after glucose infusion. The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated using the online Oxford calculator (www.dtu.ox.ac.uk/homa). The disposition index (DI) was defined as the product of insulin secretion (AIR_g) and insulin

sensitivity ($1/\text{HOMA-IR}$). To validate this combination of variables as representative of the hyperbolic relationship previously established between insulin secretion and insulin sensitivity, $\ln[\text{AIR}_g]$ was plotted against $\ln[1/\text{HOMA-IR}]$ for the 32 subjects who did not develop diabetes, and analyzed as previously described (15). This relationship was linear with a slope of -1.14 ± 0.19 that had 95% confidence limits of -0.94 and -1.35 , a range that includes -1 the theoretical value for two variables related by a rectangular hyperbola. Thus, in this data set the relationship of $\ln[\text{AIR}_g]$ and $\ln[1/\text{HOMA-IR}]$ is hyperbolic, supporting this combination in the computation of DI.

Data were analyzed using SAS v. 9.3 (SAS Institute, Cary, NC). Continuous data were summarized as median and interquartile range (IQR) for the NDM group, and individual DM patients were evaluated as being within or outside the NDM IQR. Categorical data were summarized as frequency counts. All analyses were conducted considering the subjects with NDM as a normative group and the four subjects who developed diabetes individually (DM1, DM2, DM3, and DM4).

Results

Clinical characteristics, fasting glucose and hormone measures, and results of β -cell function testing at the initial study visit for those who did (DM) and did not develop diabetes (NDM) are presented in Table I. Five adolescents who did not develop diabetes were placed on Metformin for insulin resistance before the study period and were excluded from analysis. The remaining subjects who did not develop diabetes ($n=32$) had a median age of 14.4 years (IQR 12.6, 15.7), BMI of 35.3 (IQR 29.9, 41.6), were 44% male, and had a racial/ethnic distribution of 63% Black, 31% NHW, 6% other. The five excluded from analysis controls who did not develop diabetes were predominantly female, had higher BMI, lower AIR_g and DI than the controls not on Metformin. Over four years of observation, 4 of the original 41 subjects enrolled developed diabetes (DM). All of these subjects had acanthosis nigricans before diagnosis, were Tanner stage IV or V, did not have ketoacidosis, and had family history positive for diabetes. Of the 2 subjects who had islet cell antibodies assessed, both were negative. Oral glucose tolerance tests, performed 2-3 months before entrance into the study, were normal in each of these individuals (Table II). The diagnosis of T2DM was made based on elevated fasting blood glucose and HbA1c% (DM1), and elevated fasting glucose and HbA1c% with confirmatory OGTT (DM2, DM3 and DM4).

Of the subjects who converted from normal glucose tolerance to diabetes, 3 had higher BMI than the NDM IQR, and 3 had a fasting glucose greater than 5.3 mmol/L, the top of the IQR of the NDM group. Baseline fasting insulin levels and HOMA-IR values in these subjects were also greater than the IQR of the NDM subjects. Prior to diabetes diagnosis three of the four subjects with DM had higher fasting and stimulated PI/I ratio than the NDM group. Subjects DM1 and DM2 had AIR_g values well below the 25th percentile of the NDM group at their first visit; subjects DM3 and DM4 had initial AIR_g that were in the normative range. However, the higher levels of HOMA-IR in the subjects with DM led to baseline DI for all four that was below the lower 10th percentile for the controls. Glucose disappearance during the IVGTT, k_g , was lower than all but two of the NDM group at baseline (Table I).

Measures of BMI, HOMA-IR, AIR_g, and DI over 4 years of observation are shown for the 4 subjects with DM plotted against the range for the subjects with NDM (Figure). In the subjects with NDM the trends in these measures were for increased weight gain (BMI up 9 ± 4 percent of baseline at 4 years, mean $\pm$ SEM), lesser insulin resistance (HOMA2-IR down 19 ± 8 percent of baseline), reduced AIR_g (down 35 ± 6 percent of baseline) and stable DI (97 ± 11 percent of baseline). Fasting blood glucose exceeded 5.9 mmol/L at any time in only 2 of the subjects with NDM and only persisted beyond one visit in one of these.

The key variables in the 4 subjects converting to T2DM are shown in Table III. All 4 gained weight between their baseline visit and diagnosis although the degree of weight gain varied considerably. Subject DM1 had normal fasting glucose at baseline (5.1 mmol/L), developed diabetes 5 months later and had an improved fasting glucose value at the 6 month visit following one month of metformin treatment. Subjects DM1 and DM2 had the lowest AIR_g values in the entire cohort at the beginning of the study and converted to diabetes within the first 2 years of follow up. Subjects DM3 and DM4 had AIR_g within the NDM range at study initiation and converted after 3 and 4 years. Both of these subjects had substantial weight gain over the course of the study (> 30 kg), amounts that were much more pronounced than subjects DM1 and DM2, and greater than all but two of the control subjects. However, all 4 of the subjects converting to T2DM had a $> 85\%$ decline from their initial AIR_g values within 6 months of diagnosis (Table III). HOMA-IR was substantially increased in one subject at the time of diagnosis (DM4), but values for the other 3 converters was less than, or similar to, baseline estimates. However, the combination of declining AIR_g with stable or increased insulin resistance caused markedly reduced DI for all 4 subjects developing diabetes. In fact, DI was less than the 10th percentile of the NDM group at baseline and every subsequent assessment. This coincided with steady declines in AIR_g for these subjects to give a drop in DI of $> 85\%$ of the initial value by the time of diagnosis or shortly thereafter (Table III).

Only 6 of the control subjects had a decrease in AIR_g of more than 60% over the four years of observation; in 4 of these subjects HOMA-IR also decreased such that DI was stable or improved. Two of the subjects with NDM had a reduction of DI in conjunction with a $> 60\%$ decrease of AIR_g, one by 73% and the other 66%. In one of these subjects fasting glucose increased from a baseline of 5.3 mmol/L to values > 5.7 at the 2, 3 and 4 year follow up visits. The other control subject with large reductions in AIR_g and DI maintained fasting glucose values < 5.4 mmol/L.

Discussion

The development of T2DM in adolescents seems to be progressive, as it is in adults, with gradual worsening of β -cell function in the face of insulin resistance as affected individuals pass from normal glucose tolerance to a prediabetic state (12, 16, 17). This report details the progression of 4 obese, non-diabetic adolescents from normal glucose tolerance to T2DM, and demonstrates that this transition can occur rapidly within 1-4 years. Although there were differences among the 4 subjects with DM in some biochemical and anthropomorphic characteristics, and the pace of progression to DM, they shared a low DI and rapid decline of AIR_g in the year of diagnosis; 3 of the 4 also had elevated fasting and stimulated PI/I ratios.

The decline in glucose regulation prior to diagnosis was not clearly related to changes in BMI, as these subjects experienced BMI trajectories comparable with the NDM. Moreover, HOMA-IR increased markedly in only one of these subjects at the time of diagnosis. These findings are in keeping with previous reports that impaired insulin secretion predicts future diabetes in adolescents (18) and describes for the first time an abrupt reduction in beta-cell function preceding the onset of diabetes in youth.

In this longitudinal study of insulin secretion, we selected subjects with body weights typical of adolescents developing diabetes but included only subjects with verified normal oral glucose tolerance tests in the preceding 3 months. Thus, these subjects were at greater risk for diabetes than a more general cross section of teenagers (19), but did not have the prediabetic features that mark a true high-risk group (18). We used the acute response to IV glucose as the measure of β -cell function because this is a simple, reliable test that can be performed in less than one hour, limiting the burden on subjects returning for multiple studies. AIR_g is also a sensitive marker for the development of T2DM because this function is lost early in the disease process (20). HOMA modeling is reproducible in children and adolescents (21), has been used extensively in longitudinal studies of subjects with and without diabetes (8, 22-26) and validated as reflective of changes in insulin sensitivity over time (27). We have validated the combination of AIR_g and HOMA-IR to estimate DI in our cohort and this measure best distinguished the subjects becoming diabetic. This is consistent with other studies that used alternative methods to compute DI and found this to be predictive of development of T2DM (8, 28).

In the 4 subjects with DM in this study, the transition to T2DM occurred within 1-4 years of a normal OGTT. This pace of change runs counter to the widely held view that adults progress to T2DM gradually, with affected persons spending extended periods in worsening states of prediabetes before conversion to T2DM (7, 8, 28). However, there are several studies that describe a more abrupt onset of diabetes in some adults that occurs over the relatively short period described here in our adolescents with DM (29, 30). It is not possible to determine from the small sample of teenagers and short observation period in our study whether rapid conversion from NGT to diabetes is typical in adolescents or whether a more gradual onset of disease also occurs in some individuals. There is a case report documenting the progression from NGT to prediabetes and eventually T2DM in a 10 year old girl over 5 years (31). However, longer, larger longitudinal trials would be necessary to determine the common patterns by which diabetes evolves in youth. Given the pathophysiologic insights that could be gained from understanding the natural history of T2DM in young people, and the potential for effecting prevention, such studies seem worthy to pursue.

The distinguishing feature in our subjects who developed DM was a decline in β -cell function in the period around conversion to diabetes; this was noted at the time of diagnosis in 3 subjects and 6 months after diagnosis in subject DM1 who started metformin one month before their 6 month testing. Thus, within 6 months of the diagnosis of diabetes all had decrease from baseline AIR_g of 85% or more. It is possible that some of the reduced insulin secretion measured in these subjects was a function of hyperglycemia *per se*, as the effects of glucose toxicity are well established (32). However, none of the subjects had fasting glucose values > 10.3 mmol/L at the time of diagnosis, and likely had only mild to moderate

loss of glycemic control in the period before evaluation. The subjects who developed DM were insulin resistant relative to the NDM cohort, but HOMA-IR only increased from the baseline visit in one of the four over the course of the study. Nonetheless, combined with worsening beta-cell function even stable insulin resistance likely contributed to diabetes and DI was the most consistent abnormality among the DM group, always below the normative range of the subjects with NDM. This is in keeping with the findings of longitudinal studies in adults demonstrating that DI is one of the strongest predictors of eventual diabetes (7, 8).

In addition to reduced DI, fasting glucose and the PI/I ratio were elevated at the baseline visit in the subjects with DM. Elevations of fasting glucose, within the nondiabetic range, have been reported to predict the development of T2DM in adults (30) and adolescents (17). Elevated fasting and post-stimulus proinsulin secretion is a common finding in adults with T2DM and is commonly used as a surrogate for failed or failing beta-cells (20). Elevated PI values are most pronounced in patients with severe insulin secretory defects and can be elevated up to 3-fold (33, 34). Hyperproinsulinemia is also present across the spectrum of clinically affected persons, and both adults and adolescents with impaired glucose tolerance have been reported to have increased PI/I ratios (20, 35-37). Our findings confirm those of previous studies showing that DI, fasting glucose and PI/I ratio are potential predictors of diabetes risk in obese adolescents.

Although the four subjects who developed diabetes had NGT in the period prior to their baseline visit, two already had marked impairment of AIR_g documented at their initial visit compared with the NDM group and progressed to diabetes within the year. Thus, these subjects were well on their way to beta-cell failure at the time they entered the study, suggesting that the OGTT is not a reliable predictor of impending diabetes. However, a precipitous drop of insulin secretion in the 6-12 months before diabetes diagnosis was also apparent in the remaining DM converters who started with normal AIR_g . In the NDM group, insulin secretion was generally stable, with only a small number of subjects having a reduction of AIR_g close to the level of change in the subjects with DM, and only two with a reduction of DI. In this small series initial AIR_g was predictive of the rapidity of conversion to diabetes, and a substantial decline was necessary to develop diabetes T2DM.

There are several limitations of this study. The sample size here is small and may not reflect the full spectrum of T2DM in youth. In fact, this cohort was assembled to generate longitudinal measures of β -cell function in obese, but nondiabetic, adolescents and the progression of some subjects to T2DM was unexpected. Given a background prevalence for T2DM of 0.12% derived from a population of more than 2500 comparably-aged subjects in the Cincinnati area [18], the 4 year incidence of T2DM in this study, ~ 10%, surprisingly high; this estimate may be inflated because of the extreme obesity of our study subjects (BMI = 99thile). But even though our findings are not sufficient to make definite conclusions about the epidemiology of T2DM in adolescents, they do establish that insulin secretory capacity can decline rapidly in this age group leading to diabetes. A second shortcoming in this study was the use of HOMA modeling to estimate insulin sensitivity. Although this approach has support from a range of studies, including comparisons in subjects with diabetes (22-27), lack of precision can be problematic in studies with small samples and it has not been validated in pediatric T2DM. Thus, in our small group of

subjects converting to T2DM the effect of changes in insulin resistance may not be fully appreciated. However, the within-subjects comparisons used here make it more likely that these subjects had consistent relationships between fasting glucose and fasting insulin, the key variables for HOMA, and less likely that there was bias towards underestimation of insulin resistance. Normal oral glucose tolerance may be misleading in adolescents with impending diabetes, but the disposition index, and elevated proinsulin levels may predict the transition to diabetes in some obese adolescents.

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Abbreviations

T2DM	Type 2 Diabetes Mellitus
HOMA-IR	Homeostatic model assessment of insulin resistance
PI	Proinsulin
I	Insulin
AIR_g	Acute insulin response to glucose
DI	Disposition Index
BMI	Body mass index
HbA_{1c}	Glycosylated hemoglobin percentage
IQR	Interquartile range

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Figure.

Longitudinal changes in a) BMI, b) HOMA-IR, c) AIR_g, and d) DI in 4 subjects developing T2DM over 4 years of observation (dashed lines). The range of the normal glucose tolerance subjects not developing diabetes (NDM) are depicted by the shaded area. Arrows denote the time diabetes was diagnosed.

Table 1 Characteristics of the Study Population at the initial assessment of β -cell function

	NDM		DM1	DM2	DM3	DM4
	N	Median (Q1, Q3) or Frequency				
Age, years	32	14.4 (12.6, 15.7)	19.2	14.0	12.4	15.8
Sex, n (% male)	32	14 (44%)	F	F	M	M
Race, n (%) NHW, AA, other	32	10 (31%), 20 (63%), 2 (6%)	NHW	AA	AA	NHW
BMI, kg/m ²	32	35.3 (29.9, 41.6)	55.8	43.9	34.3	43.4
Family history, n (% yes)	32	30 (94%)	Yes	Yes	Yes	Yes
Fasting Glucose (mmol/L)	31	4.8 (4.5, 5.0)	5.1	6.7	5.5	4.7
Fasting Insulin (pmol/L)	31	217.1 (171.6, 273.2)	735.4	513.0	615.3	486.7
Fasting PI/I (%)	27	10.9 (8.5, 15.7)	16.2	40.8 *	11.0	17.2
Stimulated PI/I (%)	28	2.4 (2.0, 3.5)	20.5	19.0 *	4.6	8.3
HOMA-IR	31	3.7 (3.1, 4.7)	11.8	9.2	10.2	8.0
AIR _g (min $\times$ pmol/L)	30	15763 (11674, 22951)	4345	3722	19313	12163
Disposition Index (AIR _g $\times$ 1/HOMA-IR)	30	4305 (2999, 6011)	369	406	1893	1520
Glucose Disappearance Constant, k _g (%/min)	31	-1.75 (-2.58, -1.45)	-1.21	-1.33	-1.27	-1.13

Continuous baseline data were summarized as median and interquartile range (IQR) for the non-diabetic group. Categorical data were summarized as frequency counts.

* Represents 6 month data as baseline samples not available.

Table 2

Oral glucose tolerance test results at study initiation of 4 subjects who later converted to diabetes

	Glucose (mmol/L)				Insulin (pmol/L)				HbA1c% (mmol/mol)
	0 min	30 min	60 min	120 min	0 min	30 min	60 min	120 min	
DM1	3.9	7.3	7.0	5.1	147	809	333	250	4.8 (29)
DM2	5.3	5.7	5.5	4.8	223	322	448	239	6.1 (43)
DM3	5.2	10.3	7.5	7.1	164	1648	1037	804	5.4 (36)
DM4	4.5	NA	NA	7.0	NA	NA	NA	NA	NA

NA = Not Available

Table 3

Measures of glucose tolerance in subjects developing diabetes and maintaining normal glucose levels over 4 years of observation.

Subject	Visit	Fasting Glucose mmol/L	BMI kg/m ²	Weight kg	Fasting Insulin pmol/L	AIRg	HOMA-IR	DI
†DM1	Baseline	5.1	56	145	735	4345	12	369
	6 month ^{*,#}	5.3	57	149	413	1056	7	148
	1 year	5.5	60	156	344	375	6	61
	2 year	8.1	62	158	151	535	3	174
	3 year	5.6	62	160	169	704	3	223
†DM2	4 year	7.9	63	167	170	1369	3	400
	Baseline	6.7	44	127	513	3722	9	406
	6 month	5.7	44	129	270	1411	5	287
	1 year ^{*,#}	10.3	45	131	506	856	10	86
	2 year	7.5	42	122	143	-58	3	-20
DM3	3 year	13.8	42	122	160	-113	4	-30
	4 year	14.4	42	123	165	700	3	172
	Baseline	5.5	34	91	615	19313	10	1893
	6 month	5.2	36	104	NA	NA	NA	NA
	1 year	5.6	38	114	474	8163	8	996
DM4	2 year	5.4	42	128	195	5973	4	1666
	3 year [*]	6.2	45	146	493	1801	9	207
	Baseline	4.7	43	153	487	12163	8	1520
	6 month	5.7	45	159	338	NA	6	NA
	1 year	5.0	46	164	287	7071	5	1400
NDM	2 year	6.1	48	173	2045	9445	NA	NA
	3 year	6.2	50	181	822	18	14	1
	4 year [*]	9.6	50	182	1633	-653	25	-26
	Baseline N=32	4.8 (4.5, 5.0)	35 (30, 42)	96 (80, 114)	217 (172, 273)	15763 (11674, 22951)	3.7 (3.1, 4.7)	4305 (2999, 6011)

Subject	Visit	Fasting Glucose mmol/L	BMI kg/m ²	Weight kg	Fasting Insulin pmol/L	AIRg	HOMA-IR	DI
	6 month N=31	5.0 (4.7, 5.1)	35 (29, 41)	97 (80, 118)	193 (142, 243)	14651 (7377, 22937)	3.6 (2.6, 4.3)	4747 (3023, 5981)
	1 year N=28	4.9 (4.6, 5.2)	37 (30, 42)	98 (83, 122)	168 (137, 249)	13306 (7797, 20669)	3.0 (2.5, 4.6)	4731 (3119, 6280)
	2 year N=27	5.0 (4.5, 5.2)	37 (31, 43)	104 (88, 129)	163 (93, 258)	8519 (5606, 19952)	3.0 (1.7, 4.6)	4164 (2516, 6141)
	3 year N=27	5.0 (4.8, 5.3)	35 (30, 45)	106 (77, 139)	144 (77, 227)	7534 (5022, 13830)	2.7 (1.5, 4.0)	3422 (2639, 4920)
	4 year N=25	5.0 (4.7, 5.2)	37 (30, 48)	114 (77, 143)	141 (88, 221)	8735 (5353, 14009)	2.6 (1.6, 4.0)	3858 (2826, 4911)

NDM data presented as median (25th, 75th percentile)

NA = Not Available

[†] Negative testing on islet autoimmunity panel

* Conversion to diabetes

Started metformin