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Insulin action and the development of type 2 diabetes

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This is the fourth of eight reports on the American Diabetes Association Annual Meeting and Scientific Sessions held in San Diego in June. It will cover topics related to the pathogenesis of type 2 diabetes and the mechanisms of insulin action.

Mechanisms of insulin action

In this year's Lilly lecture, Morris White, Boston, MA, discussed the development of the understanding of the mechanisms of insulin action. White described how the advent of insulin purification in 1921, the development of the insulin assay in the 1960s, and the discovery of the insulin gene in the 1970s were followed by the understanding of the tyrosine kinase activity of the insulin receptor and the isolation of its gene and an increased understanding of signal transduction and genomics. Insulin has multiple effects, which include metabolic actions on glucose, amino acid, and fatty acid uptake; long-term effects on gene expression; and inhibition of apoptosis and modulation of cell survival. Understanding of the signal transduction cascades begins with the insulin receptor, which has two binding sites, S1 and S2, that interact with and cause a conformational change in the intracellular portion of the β-subunit of the insulin receptor, which leads to its phosphorylation at three sites. Thus, the receptor itself is its own first substrate.

The question then addressed was the following: What is the second substrate? With the use of an antiphosphotyrosine antibody, a rapidly developing band was seen in gel analysis in response to a physiological range of insulin levels. The second substrate was purified and named insulin receptor substrate (IRS)-1. It was found to have >70 tyrosine phosphorylation sites, 40 serine phosphorylation sites, and 3 Src homolgy 2 (SH2) domains that modify IRS-1 to bind to phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK). PI3K causes phosphorylation of membrane lipids; this effect leads to activation of protein kinase B, which promotes protein synthesis and glucose transport and increases cell survival. Portions of the PI3K-signaling cascade could be reconstituted outside of the cell for further study.

Antibodies to IRS-1 partially react with other insulin substrates, which led to identification of IRS-2, IRS-3 (located only in adipocytes), and IRS-4 (located only in brain). 32D myeloid precursor cells lack all four types of IRS but can be modified to express these substrates and to allow exploration of their properties. For example, a truncated IRS-1 that does not activate PI3K may be shown to inhibit apoptosis in these cells by a mechanism that has yet to be discovered. IRS-1–deficient mice have decreased growth but appear otherwise normal and without diabetes, although they show evidence of peripheral insulin resistance, whereas IRS-2–deficient mice have normal growth through 30 days but develop diabetes at 10 weeks. IRS-2 deficiency impairs hepatic glycogen storage and insulin fails to decrease hepatic glucose production in these animals. Interestingly, lack of IRS-2 also impairs the β-cell expansion otherwise seen with insulin resistance. Although combined deficiency of both IRS-1 and IRS-2 is lethal, animals that lack both IRS-1 alleles and only one IRS-2 allele have increased β-cell mass, which allows compensation for the insulin-resistant state; however, those animals with only one IRS-1 allele and no IRS-2 alleles develop severe diabetes. Studies of mice heterozygous for the absence of IGF-1 and insulin receptors show that the former mediates the ability to increase β-cell mass, which suggests that there is a signaling cascade from IGF-1 to IRS-2 that mediates an antiapoptotic function and promotes β-cell survival. There is no evidence that disruption of the IRS-2 signal mediates the decreased β-cell function of human type 2 diabetes, but a hypothesis can be generated that other factors may impair the IRS-2–signaling cascades and may play roles in both type 1 and type 2 diabetes.

In addition to White's lecture, a number of related studies were presented at the meeting. Michael et al. (abstract 40) studied mice with a liver-specific insulin receptor knockout and showed that fed but not fasting hyperglycemia is associated with a 20-fold increase in fed insulin levels, which suppressed levels of triglycerides and free fatty acids by 30–50% (abstract numbers refer to the Abstracts of the 59th Annual Meeting and Scientific Sessions of the American Diabetes Association [ADA], *Diabetes* 48 [Suppl. 1]:1–A550). Kim et al. (abstract 41) and Kido et al. (abstract 42) showed that hepatocytes lacking insulin receptors, which are unable to mediate the metabolic actions of insulin, show increased growth with increased phosphorylation of IRS-1 and -2 when transfected to express IGF-1. Activation of Akt, which reflects the mitotic effect of insulin, was stimulated equally by IGF-1 and insulin receptors, whereas inactivation of GSK-3, which is related to insulin's metabolic effect, showed a greater response to insulin receptors. Izumi et al. (abstract 11) showed that insulin receptor–related receptor, an intermediary molecule located near the plasma membrane that mediates tyrosine phosphorylation of IRS-1 and -2, is expressed in

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Abbreviations: ADA, American Diabetes Association; AN, acanthosis nigricans; APS, adapter protein and substrate; CPT, carnitine palmitoyltransferase; GADA, GAD antibody; HNF, hepatocyte nuclear factor; ICA, islet cell antibody; IRAP, insulin-responsive aminopeptidase; IRS, insulin receptor substrate; MAPK, mitogen-activated protein kinase; MODY, maturity-onset diabetes of the young; mtDNA, mitochondrial DNA; PI3K, phosphatidylinositol 3-kinase; SH2, Src homology 2; TNF-α, tumor necrosis factor-α; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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pancreatic β-cells and plays a role in the regulation of β-cell mass. Bonner-Weir et al. (abstract 9) reported that mice lacking IRS-2 show a decrease in islet mass with normal replication but an increase in apoptosis of β-cells and normal insulin secretion in response to glucose.

Zisman et al. (abstract 43) produced mice with selective disruption of GLUT4 expression in skeletal and cardiac muscle. In vitro, muscle from these mice showed a 72–88% decrease in basal muscle glucose uptake and absent response to insulin. In vivo, hyperglycemia and severe insulin resistance were seen. Abel et al. (abstract 44) studied heart muscle obtained from transgenic knockout mice with cardiac-specific deletion of GLUT4. In adipose tissue, heart, and skeletal muscle, GLUT4 is targeted to intracellular membrane vesicles, which contain several membrane proteins in addition to GLUT4, with insulin-responsive aminopeptidase (IRAP) completely colocalized with GLUT4 in both basal and insulin-treated cells. The absence of GLUT4 eliminated IRAP in intracellular vesicles, suggesting that GLUT4 expression is required for the formation of the insulin-sensitive vesicular compartment. Because GLUT4 itself and IRAP are proteins present in intracellular vesicles and contain dileucine motifs, Brownell et al. (abstract 45) inhibited clathrin-adapter protein complexes using cell-permeable dileucine peptides. GLUT4 endocytosis was inhibited with marked stimulation of glucose uptake, partially independent of insulin receptor activation. Kanzaki et al. (abstract 47) studied a trimeric guanosine 5′-triphosphate–binding protein, Gq-α, to show that it potentiates insulin-stimulated GLUT4 translocation to the plasma membrane. In a study on the relationship between GLUT4 and fiber type in human muscle, Gaster et al. (abstract 96) showed that levels of GLUT4 decrease from age 29 to 64 years and are higher in slow fibers than fast fibers at both ages.

Krook et al. (abstract 94) compared the metabolic and mitogenic events after insulin administration in vitro in skeletal muscle from 12 people with type 2 diabetes with those in skeletal muscle from 17 control subjects. Protein expression of the insulin receptor, IRS-1, IRS-2, MAPK, and glycogen synthase, insulin-induced tyrosine phosphorylation of the insulin receptor β-subunit, and insulin-stimulated activity of MAPK and glycogen synthase were similar, whereas tyrosine phosphorylation of IRS-1 was reduced by 40% and antiphosphotyrosine-associated PI3K was decreased by 45–49% in the type 2 diabetic subjects; these effects were in association with impaired insulin-stimulated muscle glucose transport. Carvalho et al. (abstract 98) showed that IRS-1 protein expression and associated PI3K activity were 70% lower in adipocytes from individuals with type 2 diabetes, and that 30% of healthy nondiabetic individuals with at least two first-degree relatives with type 2 diabetes and 30% of individuals with severe obesity had low levels of adipocyte IRS-1 protein and mRNA expression in association with insulin resistance and higher fasting insulin and triglyceride levels.

Withers et al. (abstract 102) studied mice lacking one or two IRS-1 and/or IRS-2 genes and showed that *1*) double heterozygotes have hyperinsulinemia and mild fasting hyperglycemia, *2*) mice that have no IRS-1 alleles and lack one IRS-2 allele have growth retardation and insulin resistance with β-cell compensation, and *3*) mice that have no IRS-2 alleles and lack one IRS-1 allele have severe insulin deficiency with hyperglycemia, which suggests mitogenic versus metabolic function of the two peptides. Previs et al. (abstract 217) showed that mice lacking IRS-1 had adipose tissue insulin action similar to controls with decreased action in muscle, whereas those mice that also lacked IRS-2 also had decreased insulin suppression of lipolysis. Higaki et al. (abstract 277) showed that mice lacking IRS-2 but without severe hyperglycemia show muscle glucose uptake at levels similar to those of controls, which suggests that the decrease in muscle glucose uptake in hyperglycemic mice that lack IRS-2 is actually a manifestation of glucose toxicity rather than a direct reflection of the action of IRS-2 in muscle. Pillay et al. (abstract 103) described the adapter protein and substrate (APS), a tyrosine-kinase substrate found in adipose tissue, liver, and skeletal muscle, and physiological targets of insulin action. APS contains an SH2 domain that binds with high affinity to the insulin receptor cytoplasmic domain after autophosphorylation but does not interact with IRS proteins or the EGF receptor. These observations suggest that APS is an alternative adapter protein that mediates insulin action. Kitamura et al. (abstract 104) showed that regulation of cyclic nucleotide phosphodiesterase 3B by insulin involves a phosphorylation step mediated by the serine-threonine kinase Akt–protein kinase B.

Pathogenesis of type 2 diabetes

Rondinone and Pederson (abstract 961) extended previous studies that showed decreased IRS-1 protein expression in adipocytes from individuals with type 2 diabetes in comparison with both healthy and type 1 diabetic subjects. Treatment of adipocytes with insulin in vitro mimicked these characteristics, whereas administration of vanadate inhibited the tyrosine dephosphorylation of IRS-1 and decreased its degradation, which appeared to involve PI3K. Frayling et al. (abstract 142) found abnormalities of the insulin promoter factor-1 gene, a cause of maturity-onset diabetes of the young (MODY), in 3 of 36 individuals with type 2 diabetes. In a larger group, the mutations were found in 7 of 210 type 2 diabetic patients vs. 5 of 512 individuals without diabetes, although the 5 nondiabetic subjects had higher 2-h glucose levels than the overall group during an oral glucose tolerance test. Federici et al. (abstract 143) reported that the $Gly^{972} \rightarrow Arg$ polymorphism of IRS-1, which is more prevalent in patients with type 2 diabetes, does not alter the extent of insulin-stimulated tyrosine phosphorylation of IRS-1 but decreases serine phosphorylation of Akt, which is activated by PI3K, and is associated with a 21–46% increase in apoptosis of β-cells; these findings suggest decreased serine phosphorylation of Akt in type 2 diabetic patients may be a mechanism by which β-cell mass is decreased.

Hashim et al. (abstract 802) found that 1–4% of diabetic patients had hepatocyte nuclear factor (HNF)-1α mutations similar to those of type 3 MODY. More evidence of genetic patterns associated with type 2 diabetes is emerging. The strategy of determining all genes in a chromosomal area associated with diabetes may eventually allow better understanding of the mechanisms involved. St. Jean et al. (abstract 196) performed a genome-wide scan in >800 individuals from the Old Order Amish of Lancaster County, Pennsylvania, including 83 who were found to have diabetes and showed evidence of linkage in chromosomal regions 1p, 2p, 2q, and 14q. Ehm et al. (abstract 198) analyzed samples collected in the ADA's Genetics of NIDDM Study. In collected samples from 497 Caucasian, 365 Mexican American, 229 African-American, and 128 Japanese American subjects, these investigators found evidence of genes that contribute to type 2 diabetes at regions of chromosome 5 and at a region of chromosome 12 that contains the MODY type 3

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gene, HNF-1α. Watanabe et al. (abstract 197) sampled 2,095 subjects, 1,240 of whom had diabetes, from 580 families in a Finnish cohort. Sites for acute insulin response on chromosome 10, for elevated fasting insulin and fasting glucose on chromosome 14, and for elevated 2-h glucose on chromosome 20 were found. Duggirala et al. (abstract 199) studied genetic correlates of insulin resistance from 310 nondiabetic individuals from 27 Mexican American families and showed linkage of fasting insulin with markers on chromosomes 4 and 6. Wolford et al. (abstract 200) presented a molecular analysis of a region on chromosome 1q21-q23 that is linked to type 2 diabetes in Pima Indians and in a Caucasian population and reported that a gene linked to familial partial lipodystrophy may be the mediator of the association. Bektas et al. (abstract 201) screened 233 diabetic and 152 nondiabetic family members from 32 families with early-onset autosomal-dominant type 2 diabetes and found a diabetes locus on chromosome 12q that is distinct from a previously reported location.

Kousta et al. (abstract 99) compared 39 euglycemic women with a history of gestational diabetes with 50 control women who were matched for age, parity, and time since delivery. The 39 women who had a history of gestational diabetes showed preservation of β-cell function with insulin resistance in frequently sampled intravenous glucose tolerance tests and fourfold higher fasting insulin levels with increased triglyceride levels and waist-to-hip ratios. Resting energy expenditure was similar between the groups, but postprandial thermogenesis was 18% lower in the women who had gestational diabetes, which could potentially contribute to obesity. Morton et al. (abstract 721) compared 339 middle-class African-American women from the Health Assessment Study of African-American Women with 923 middle-class Caucasian women from the Rancho Bernardo Study. The African-American women and the Caucasian women had similar heights and waist-to-hip ratios, but the African-American women had higher BMI, weight, percentage of body fat, and lean body mass. The African-American women also had higher systolic blood pressure, fasting plasma glucose levels, and fasting and postchallenge insulin levels, but they had lower total cholesterol, HDL cholesterol, and triglyceride levels and a lower (34 vs. 40%) prevalence of abnormal glucose tolerance. Araneta and Wingard (abstract 723) compared 240 Filipina with 380 Caucasian women, aged 50–69 years, who showed 37 vs. 8%, respectively, prevalence of diabetes and found waist circumference to be the strongest predictor in both populations. Tumor necrosis factor-α (TNF-α) may mediate insulin resistance in obesity and diabetes and decreases tyrosine autophosphorylation of the insulin receptor and IRS-1 in adipose tissue. Kono et al. (abstract 343) reported that osteoblast function, which was evaluated by measuring serum levels of carboxylated osteocalcin, was negatively correlated with plasma glucose levels and insulin sensitivity in 28 patients with type 2 diabetes. Serum soluble TNF-α receptor, an index of TNF-α action, was higher in diabetic patients than normal control subjects and negatively correlated with carboxylated osteocalcin levels. Aljada et al. (abstract 137) showed that insulin increases and that TNF-α decreases nitric oxide synthase activity in endothelial cells, which could potentially contribute to cardiovascular disease.

Casanova-Romero et al. (abstract 726) reported an association of both acanthosis nigricans (AN) and acrochordons (or skin tags) with obesity and with insulin resistance independent of glucose tolerance. Both AN and acrochordons were less frequent in the non-Hispanic Caucasian population than in the Hispanic and African-American populations. After examining 1,800 Cherokee Indians who participated in the Cherokee Diabetes Study, Lee et al. (abstract 727) concluded that AN is a useful marker for diabetes by noting that the prevalence rates of obesity, hyperinsulinemia, and diabetes are significantly higher in those patients with AN. Burke et al. (abstract 728) studied examined 365 Hispanic individuals from 31 families and showed a similar association between AN and type 2 diabetes, as well as with risk factors such as BMI, waist circumference, blood pressure, and fasting insulin. Hale et al. (abstract 121) reported a 19% prevalence of AN among 474 Mexican American children aged 11–14 years; the prevalence of AN among these children was particularly associated with greater body weight. Everts and Berdanier (abstract 23) showed that BHE/Cdb rats, which mimic humans with mitochondrial diabetes, required three times as much retinyl palmitate as controls after depletion of vitamin A for 18 weeks, which suggests that vitamin A plays a role in mitochondrial function and gene expression and that abnormalities of this system may be related to diabetes. Sakurai et al. (abstract 719) reported an association between sleeping <6 h nightly and insulin resistance, regardless of age and BMI, based on the evaluation of fasting glucose and insulin levels among 1,418 Japanese males without diabetes.

A fascinating area of research has concerned the relationship between low birth weight and the insulin resistance syndrome. Eriksson et al. (abstract 311) reported future risk of type 2 diabetes negatively associated with birth weight and independently and positively associated with BMI at ages 11 and 15 years among 7,088 individuals born between 1924 and 1933. In the highest BMI quartile at age 14 years, the cumulative risks of diabetes among men and women in the lowest birth weight quartile were 14.9% in men and 13.8% in women vs. 4.9% in men and 4.5% in women in the highest birth weight quartile. Park et al. (abstract 309) noted that fetal undernutrition is associated with insulin resistance in later life and that decreased mitochondrial DNA (mtDNA) content in peripheral blood both precedes the development of diabetes and is inversely correlated with insulin resistance parameters, such as diastolic blood pressure and waist-to-hip ratio. In light of their earlier finding that mothers with lower levels of peripheral blood mtDNA give birth to infants with low birth weight, these investigators studied an animal model of fetal undernutrition, and found lower mtDNA content in liver and muscle. Maianu et al. (abstract 1202) fed rats low- or high-protein diets during pregnancy to produce low birth weight offspring and found that, during adulthood, their skeletal muscle expression of GLUT4 and carnitine palmitoyltransferase (CPT)-1, the rate-limiting enzyme for mitochondrial long-chain fatty acid oxidation, was reduced, although CPT-1 was reduced more in gastrocnemius than heart, and GLUT4 was decreased in muscle but increased in adipocytes.

Another important cause of insulin resistance is the use of protease inhibitors by HIV-1–infected patients. Behrens et al. (abstract 348) examined 38 treated patients and 17 nontreated patients. Of the treated and nontreated patients, 46 vs. 24% had impaired oral glucose tolerance, and 13 vs. 0%, respectively, had diabetes. Of the treated patients, 71% had dyslipidemia. Vigouroux et al. (abstract 349) consecutively evaluated 192 HIV-1^+ patients treated with protease inhibitors and found

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peripheral lipoatrophy in 70% and increased cervical or abdominal fat in 64% of the patients. Abnormal glucose tolerance or insulin resistance was seen in 59% of the patients with one of these forms of lipodystrophy vs. 37% with no form of lipodystrophy. HIV viral load, CD4 count, and serum TNF-α did not differ significantly between the two groups. Sinclair and Welch (abstract 1518) reached a different conclusion from their study of 166 HIV-1^+ patients. Of the 19 patients with diabetes, 14 had preexisting diabetes, and 5 became diabetic after protease inhibitors were initiated, which suggests that receiving protease inhibitor therapy did not affect the new onset of diabetes in this population of HIV-1^+–infected patients.

Type 2 diabetes in the young

Kwamura et al. (abstract 729) used the capture-recapture method to study the prevalence rate of childhood type 2 diabetes in children from Osaka, Japan, examining material from three sources: documents of the medical benefits system, urine glucose screening in school, and a questionnaire sent to 198 hospitals in Osaka. From the respective sources, Kwamura et al. identified 13, 9, and 10 children as having type 2 diabetes. The ascertainment rates of the three sources were 45, 31, and 35%, respectively, for a total of 44 patients, and the prevalence rate of type 2 diabetes was 28.6 per 100,000 children, which is more than four times that previously suggested. Dean (abstract 730) reported on 82 First Nation Cree-speaking children (80% female) aged 6–17 years, who were diagnosed with type 2 diabetes and were referred since 1981 to the only pediatric diabetes clinic in Winnipeg, Manitoba, Canada. From 1981 to 1985, the mean number of referred cases per year was 0.8. That number increased to 8.4 cases/year from 1994 to 1998 for a current minimum annual age-specific incidence of 41/100,000 and a prevalence of 1.37/1,000, although actual rates of prevalence in the rural areas of Winnipeg may be tenfold greater. Jones et al. (abstract 350) reported 58 children and adolescents with new-onset diabetes. Those children from ethnic minorities especially, with obesity, with a family history of type 2 diabetes, and with AN were suspected of having type 2 diabetes. The diagnosis was confirmed by finding no immune markers for type 1 diabetes, by finding normal or elevated plasma insulin or C-peptide levels, and by observing responses to extended treatment with diet with or without oral antihyperglycemic drugs. Of the study population, 53% were Mexican Americans and 19% were African-Americans vs. 20 and 6%, respectively, of the general population (as determined by the 1990 San Diego County census). AN was found in 74% of the study population, and 83 and 59% of the study population had BMI at diagnosis above the 90th and 95th percentiles, respectively, for age and sex. Vargas et al. (abstract 361) reported on 19 patients in New York, NY, who presented at age 10–17 years with mean BMI 37 kg/m^2, with mean serum insulin levels 77 mIU/l, or with mean C-peptide levels 5.5 ng/dl. Of the 19 patients, 42% presented with unrecognized hyperglycemia, and 58% had symptoms of polyuria. The mean initial glucose level was 397 mg/dl, and the mean HbA_{1c} concentration was 9.3%; of the patients, 47% were Hispanic and 37% were African-American; all of the patients had AN; of 16 patients with available family histories, 14 had first- or second-degree relatives with type 2 diabetes. Young et al. (abstract 375) reported on 76 children in Cincinnati, OH, who presented with diabetes, of whom only 1 was prepubertal. African-American females typically presented with diabetes after the completion of puberty, whereas Caucasian females and males of both racial groups presented throughout the entire range of puberty.

Pinero-Pilona et al. (abstract 352) reported on a 4-year follow-up of 29 individuals from Dallas, TX, who presented with clinical features of type 1 diabetes, in particular ketoacidosis, but did not require long-term insulin therapy after a variable period of follow-up; this pattern is referred to as type 1.5 diabetes. The patients presented with an average BMI of 33.8 kg/m^2 and with polydipsia, polyuria, weight loss averaging 12.8 kg, and ketosis or ketoacidosis. All of the patients were islet cell antibody (ICA)-, GAD antibody (GADA)-, and insulin autoantibody–negative without DR3 or DR4. Of the 29 patients, 18 were African-American, 8 were Hispanic, and 3 were Native American. The average age was 34 years, and mean GHb concentration was 20% at diagnosis. Those who regained lost weight decreased mean GHb level to 9.9%, whereas continued weight loss was associated with a mean GHb level of 20.3%. Aizawa et al. (abstract 360) reported on nine patients in Matsumoto, Japan, between the ages 16 and 36 years who presented similarly with ketosis or ketoacidosis, an average 11-kg weight loss, and the absence of negative ICA and GADA and did not need insulin 3 months after diagnosis. "Existence of such diabetes," Pinero-Pilona et al. commented, "exemplifies complexity of human diabetes and casts strong doubt on the dichotomic etiologic division of common diabetes into type 1 and type 2."

Glucose tolerance testing

Weyer et al. (abstract 116) studied 17 Pima Indian patients over a 5-year period. They observed 12 and 27% decreases in insulin-stimulated glucose disposal and in the acute insulin response to intravenous glucose during the change from normal to impaired glucose tolerance and further 19 and 51% decreases during the change from impaired glucose tolerance to the development of diabetes. Body weight increased 6 and 8% with each change, which are increases similar to those in patients who did not progress to diabetes, but the nondiabetic group did not show worsening insulin secretion and sensitivity. Weyer and Pratley (abstract 119) compared 83 nondiabetic Pima Indians who had either normal fasting glucose levels (<110 mg/dl) or impaired fasting glucose levels (110–125 mg/dl) and either normal 2-h glucose levels (<140 mg/dl) or impaired 2-h glucose levels (140–199 mg/dl). The group with normal fasting and increased 2-h glucose levels and the group with increased fasting and normal 2-h glucose levels had similar degrees of insulin resistance and deficiency. Those patients with the combined defects had correspondingly greater degrees of metabolic abnormality. Larrson and Ahren (late-breaking abstract 25) prospectively studied glucose tolerance in 86 women aged 58–59 years. After 3 years, 28 of the patients had developed impaired glucose tolerance; those patients had greater baseline insulin resistance and a lesser insulin response to arginine (corrected for the degree of baseline insulin resistance) but a greater glucagon response. As part of the Insulin Resistance Atherosclerosis Study, Wagenknecht et al. (abstract 755) similarly reported that both insulin resistance and low acute insulin response predict type 2 diabetes.

Leiter et al. (abstract 705) screened 9,042 patients of Canadian family physicians for random glucose levels >100 mg/dl. Of the patients screened, 2.2 and 1.6% had fasting glucose levels >126 and 140 mg/dl, and another 3.5% had fasting glucose levels 110–125 mg/dl. Low HDL cholesterol levels, high triglyceride levels, hypertension, and heart disease were more

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common in both groups, which attests to the validity of routine screening of patients >40 years old with casual finger-prick blood-sugar determination. Davidson et al. (377) reported that glucose tolerance data from pooled population surveys of 8,915 subjects and of 2,836 subjects in the National Health and Nutrition Evaluation Survey III showed that two of three individuals with 2-h glucose levels 200–239 mg/dl, but only one of five of those with 2-h glucose levels >240 mg/dl have normal HbA_{1c} levels, which suggests that it may be more valid to diagnose diabetes above the latter level. Perry et al. (abstract 383) characterized 61 patients with newly diagnosed diabetes on the basis of 2-h oral glucose tolerance test levels ≥200 mg/dl; all of the patients had fasting glucose levels >110 and <140 mg/dl. At 2- to 4-week follow-up, only 53% had fasting glucose levels >126 mg/dl, giving a sensitivity of 22%. Only 38% had both fasting glucose levels >126 mg/dl and HbA_{1c} levels >6.1%. Having either fasting glucose levels >126 mg/dl or HbA_{1c} levels >6.1%, however, had a sensitivity of 72.2%, which suggests that determination of HbA_{1c} levels may be a better screening strategy to detect early diabetes.

Wat et al. (abstract 707) reported on glucose tolerance findings in 2,775 Chinese subjects. Of the study population, 2,475 had fasting glucose levels <110 mg/dl, which is considered to be normal according to the 1997 ADA criteria, but 15% had 2-h glucose levels between 140 and 199 mg/dl, and 2.3% had 2-h glucose levels ≥200 mg/dl in association with higher BMI, waist-to-hip ratio, blood pressure, triglyceride levels, LDL cholesterol levels, and lower HDL cholesterol levels. These data support the 1998 World Health Organization (WHO) recommendation that glucose tolerance testing should be performed with fasting glucose levels <126 mg/dl. Likewise, Cohen et al. (abstract 1735) reported that in a high-risk population with 171 individuals given oral glucose tolerance testing, 23 and 22% had impaired glucose tolerance and diabetes, but the use of fasting glucose levels ≥126 mg/dl had sensitivity, specificity, false negative, and positive predictive value values of 50, 92, 50, and 8%, respectively, which suggests that fasting glucose testing is not an adequate screening tool. Kousta et al. (abstract 712) reported that glucose tolerance test findings on the basis of fasting glucose levels, which is in accord with the 1997 ADA guidelines, in 165 women with prior gestational diabetes showed that 11% had impaired glucose tolerance and 12% had diabetes. However, on the basis of the 1999 WHO glucose tolerance test criteria, 30% had impaired glucose tolerance and 15% had diabetes, which suggests overly low sensitivity of the 1997 ADA fasting glucose guidelines. Gabir et al. (abstract 711), however, reported that among 2,743 Pima Indians who had glucose tolerance testing and 5-year follow-up, the lower 85%, the middle 10%, and the upper 5% of each fasting glucose distribution had diabetes-development rates of 4, 18, and 37%, respectively. These data are almost identical to the diabetes-development rates in the lower 85%, the middle 10%, and the upper 5% of each 2-h glucose distribution (4, 17, and 39%).

From a study of 3,075 adults aged 70–75 years, Resnick et al. (abstract 724) found that mean HbA_{1c} levels were 7.7% in 100 patients with fasting glucose levels >126 mg/dl, 6.6% in 48 patients with fasting glucose levels between 110 and 126 mg/dl but with 2-h postglucose levels >200 mg/dl, 6.3% in 120 patients with fasting glucose levels between 110 and 126 mg/dl alone, and 6.1% in 93 patients with 2-h glucose levels >200 mg/dl alone. Resnick et al. commented that if the fasting glucose is considered the standard for identifying diabetes, then a subset of older adults who are classified as nondiabetic will have metabolic abnormalities comparable to those of individuals with undiagnosed diabetes and may therefore have similar adverse outcomes. A number of reports gave interesting information in regard to the outcome for individuals diagnosed with diabetes on the basis of fasting and 2-h glucose levels. Vaccaro et al. (abstract 746) reported the risk of diabetes in 1,233 telephone company employees aged 40–59 years who were evaluated by oral glucose tolerance testing in 1980. Of these employees, 7.2% had impaired glucose tolerance vs. 3.2% with impaired fasting glucose with only a 41% overlap because of the frequency of postload hyperglycemia with normal fasting glucose. Of those with impaired glucose tolerance, 33%, compared with 7.2% of those with impaired fasting glucose, progressed to diabetes over a period of 11.5 years. Sorkin et al. (abstract 710) reported on a 13-year median follow-up of 1,064 men in the Baltimore Longitudinal Study of Aging and compared fasting glucose and glucose tolerance testing classifications of impaired glucose tolerance and diabetes. Those patients with normal or impaired fasting glucose levels but normal oral glucose tolerance had no increase in mortality, whereas those subjects with normal fasting glucose levels who had diabetes or impaired glucose tolerance as determined by glucose tolerance testing had a 30 and 39% increase in risk, respectively. Tuomilehto et al. (abstract 713) presented pooled glucose tolerance test and mortality data on 24,658 patients from 14 prospective European studies. Within each category of fasting glucose, mortality increased with increased 2-h glucose levels, but, for the 2-h glucose categories, impaired glucose tolerance, and diabetes, there was no increase in mortality with increasing fasting glucose levels. The excess mortality rates of men and women with impaired fasting glucose were increased by 21 and 12%, whereas for those with impaired glucose tolerance, the rates were increased by 49 and 50%. Kashyap et al. (abstract 393) compared 18 newly diagnosed male patients over the age of 60 years with fasting serum glucose levels between 126 and 140 mg/dl with 12 age-matched nondiabetic individuals with normal fasting serum glucose levels. The prevalence rates of retinopathy and microalbuminuria were significantly higher in the diabetic patients, affirming the validity of lowering the diagnostic fasting glucose level to 126 from 140 mg/dl.

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