THOMSON HEALTHCARE

CLINICAL INSIGHTS® IN
Diabetes

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NDEI NATIONAL DIABETES EDUCATION INITIATIVE™
FOR HEALTHCARE PROFESSIONALS

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Sponsor

This educational activity is a component of the *National Diabetes Education Initiative*® (NDEI®), sponsored by Thomson Professional Postgraduate Services® (PPS), Secaucus, NJ.

Clinicians who wish to receive CME credit for this educational activity should do the following: (1) read the current issue; (2) review the original articles discussed in their entirety; and (3) complete the post-test and evaluation form included to conclude this CME activity. You may also complete the post-test and evaluation form on our website, www.ndei.org. To apply for CME credit, return the completed post-test and evaluation form to:

Thomson Professional Postgraduate Services®
CME Dept. T177
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You may also fax the completed materials to 1 (201) 430-1441 or complete the post-test and evaluation form online. If you have any questions, please call 1 (800) 606-6106 Ext. 6126.

Applicants will receive a certificate of participation from PPS by return mail within 6 to 8 weeks of the date of receipt of the completed evaluation form and post-test. Online applicants will automatically receive their CME credit certificate upon completion of the online post-test and evaluation form.

Target Audience

This educational activity is designed for primary care physicians, internal medicine specialists, endocrinologists, diabetologists, cardiologists, and other healthcare professionals involved in the care and management of patients with type 2 diabetes, insulin resistance, and cardiovascular disease.

Learning Objectives

After studying the literature presented in this *Clinical Insights*® *in Diabetes* series, participants should be better able to:

- Identify patients with type 2 diabetes and the metabolic syndrome
- Select an appropriate therapeutic regimen for patients with type 2 diabetes and the metabolic syndrome
- Summarize risk factors for cardiovascular disease in patients with type 2 diabetes and the metabolic syndrome

Accreditation

Thomson Professional Postgraduate Services® is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Thomson Professional Postgraduate Services® designates this educational activity for a maximum of .50 *AMA PRA Category 1 Credit*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Application for CME credit has been filed with the American Academy of Family Physicians. **Determination of credit is pending.**

Grantor

This CME activity is supported by an unrestricted educational grant from Takeda Pharmaceuticals North America, Inc.

SILVIO E. INZUCCHI, MD,* CO-EDITOR-IN-CHIEF; THOMAS A. BUCHANAN, MD,† REVIEWER; TERRENCE F. FAGAN,‡ MANAGING EDITOR; MARK PALANGIO,§ WRITER

Is Measuring Waist Circumference a Better Indicator of Insulin Resistance Than Other ATP-III Metabolic Syndrome Components?

The metabolic syndrome is a group of risk factors for coronary heart disease (CHD). The National Cholesterol Education Program's Adult Treatment Panel III (ATP-III) definition of the metabolic syndrome is the most widely used in the United States and requires 3 or more of the following components: high waist circumference, high fasting glucose value, low high-density lipoprotein (HDL) cholesterol level, high triglyceride level, and high blood pressure. Such components occur more frequently among insulin-resistant individuals who might be at increased risk for CHD beyond that determined by low-density lipoprotein cholesterol levels.

Sierra-Johnson and colleagues evaluated the accuracy of the ATP-III metabolic syndrome definition in identifying insulin-resistant individuals. The study group consisted of 256 non-Hispanic white subjects from the Rochester (Minnesota) Family Heart Study who were without treated hypertension or diabetes (123 men and 133 women; mean age, 39.1 years; age range, 20 to 60 years). Insulin resistance (IR) was assessed by frequently sampled intravenous glucose tolerance tests (FSIVGTT) and IR was defined as being in the lowest quarter of insulin sensitivity for the cohort. Receiver operating characteristic curves were plotted to illustrate the relationship between false-positive and true-positive detection rates for counting of categorical metabolic syndrome components.

The prevalence of metabolic syndrome was 15.6% (16.2% in men and 15.1% in women; P=0.465). For identifying IR, the ATP-III metabolic syndrome criteria conferred low sensitivity (42% overall; 45% in men; 39% in women; sex difference, P=0.137) but high specificity (94% overall; 93% in men; 95% in women; sex difference, P=0.345). By requiring 2 rather than 3 metabolic syndrome components, sensitivity increased to 70%, whereas specificity decreased to 78%.

Using the area under the receiver operating characteristic curve (AUC) to compare accuracies in detecting IR, the diagnostic accuracy of counting ATP-III metabolic syndrome components was fair (AUC=0.768 overall; 0.797 in men; 0.747 in women). However, considering waist circumference alone as a quantitative trait improved diagnostic accuracy (AUC=0.906 in men, P=0.001; AUC=0.822 in women, P=0.10) and was equivalent to counting metabolic syndrome components for the overall group (AUC=0.813). Triglyceride concentration was the only other single component to confer greater accuracy than counting metabolic syndrome components (AUC=0.794 overall; 0.806 in men; 0.806 in women). Blood pressure, glucose value, and HDL-C concentration individually provided less predictive value.

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See Page 3 for Details.

The main limitation of this study is that these findings might only be relevant to healthy white adults without type 2 diabetes.

These results indicate that the application of the ATP-III metabolic syndrome criteria offer high specificity but low sensitivity for screening asymptomatic white adults for IR. The study investigators suggest that measuring waist circumference might be a more accurate means for detecting IR than counting metabolic syndrome components, as advocated by ATP-III guidelines.

Sierra-Johnson J et al. Correspondence between the Adult Treatment Panel III criteria for metabolic syndrome and insulin resistance. *Diabetes Care*. 2006;29:668-672.

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COMMENTARY

THOMAS A. BUCHANAN, MD, Professor of Medicine, Obstetrics and Gynecology, and Physiology and Biophysics at the University of Southern California Keck School of Medicine, Los Angeles, California.

The paper by Sierra-Johnson et al demonstrates that most non-Hispanic white people who meet ATP-III criteria for the metabolic syndrome are insulin resistant (ie, are among the lowest 25% of people for insulin sensitivity as measured directly with an IV glucose tolerance test), while many insulin-resistant individuals do not meet those ATP-III criteria. These findings are consistent with prior reports. The study also demonstrates that waist-circumference measurements provide somewhat better sensitivity and specificity for detection of insulin resistance (IR) than does diagnosing the metabolic syndrome. What are the messages for clinicians in these findings? One message could be that if you want to find IR, measure the waist circumference. Unfortunately, the authors don't provide the actual waist circumferences and their predictive values for IR; therefore, it is difficult to know how to apply their findings to clinical practice. Even if they had provided the circumferences, applicability to other ethnic groups would be limited. Most importantly, the paper raises the question of why clinicians should look for IR in the first place. If subjects are insulin resistant but don't have evidence of comorbid conditions (eg, components of the metabolic syndrome), then of what importance is detection of their IR? There is currently no evidence that treating isolated IR has any impact on morbidity or mortality. Even if components of the metabolic syndrome co-exist with IR, treatment of the IR may not be the best approach. For example, hypertension is affected little if at all by treatments (eg, thiazolidinediones) that have large effects to ameliorate IR.

Until the specific mediators of comorbidities of obesity that have come to be called the metabolic syndrome are identified and until treatments to reduce the comorbidities through those mediators are available, clinicians should identify and treat the components of the metabolic syndrome individually, not as if they were a single disease. In doing so, clinicians can be encouraged by the knowledge that most of the components of the metabolic syndrome (blood pressure, glucose, lipids) are identified by routine care in older adults. Measurement of body mass index (BMI) and waist circumference may identify younger individuals who also need testing. Standards for at-risk BMI or waist circumference should be appropriate for the ethnicity of the patient. Treatments should be evidence based and directed at specific diseases or risk factors rather than at some as yet poorly understood syndrome.

Men with higher testosterone levels had a 42% lower risk for type 2 diabetes compared with those with lower concentrations.

Differences of Endogenous Sex Hormones in Men and Women Linked to Type 2 Diabetes Risk

Type 2 diabetes increases the risk of coronary heart disease mortality in both men and women, but the risk is more pronounced in women. Incomplete findings suggest that endogenous sex hormones might play different roles in the development of type 2 diabetes in men and women.

Through a systematic review and meta-analysis, Ding and associates evaluated the association of plasma levels of testosterone, sex hormone-binding globulin (SHBG), and estradiol with the risk of type 2 diabetes. A search of EMBASE and MEDLINE (1966-June 2005), references of retrieved articles, and direct author contact identified 43 prospective and cross-sectional studies involving type 2 diabetes that presented relative risks (RRs) or hormone levels for cases and controls. These studies included a total of 6,974 women and 6,427 men. This analysis pooled data using random effects and meta-regressions.

In cross-sectional studies, testosterone level was significantly lower in men with type 2 diabetes (mean difference, –76.6 ng/dL; 95% confidence interval [CI], –99.4 to –53.6) and higher in women with type 2 diabetes (mean difference, 6.1 ng/dL; 95% CI, 2.3 to 10.1) compared with controls ($P<0.001$ for sex difference). The sex-dependent differences in testosterone level remained significant after adjustment for age, race, and diabetes diagnosis criteria, as well as internal control for body mass index and waist-to-hip ratio. Analysis of prospective studies with men also found lower testosterone levels among incident cases (mean difference, –71.5 ng/dL; 95% CI, –116.4 to –26.8). Furthermore, prospective studies demonstrated that men with higher testosterone levels (range, 449.6 to 605.2 ng/dL) had a 42% lower risk for type 2 diabetes (RR, 0.58; 95% CI, 0.39 to 0.87) compared with those with lower concentrations (range, 213.2 to 446.7 ng/dL). Limited data suggest a sex dimorphism for the link between total testosterone and type 2 diabetes ($P=0.06$ for sex difference).

In both cross-sectional and prospective studies, SHBG was more protective in women than in men ($P\leq0.01$ for sex difference for both). Prospective studies showed that women with higher SHBG levels (>60 vs ≤60 nmol/L) had an 80% lower risk of type 2 diabetes (RR, 0.20; 95% CI, 0.12 to 0.32), whereas men with higher SHBG levels (>28.3 vs ≤28.3 nmol/L) had a 52% lower risk of type 2 diabetes (RR, 0.48; 95% CI, 0.34 to 0.69) ($P=0.003$ for sex difference).

In cross-sectional studies, estradiol levels were elevated in both men and postmenopausal women with type 2 diabetes compared with controls (mean difference, 3.5 pg/mL; 95% CI, 0.94 to 6.0; $P=0.007$). There was no apparent sex dimorphism in estradiol levels ($P=0.87$).

The results of this systematic review indicate that endogenous levels of testosterone influence the risk of developing type 2 diabetes in opposite directions in men and women and that SHBG is associated inversely with diabetes risk in both genders, although somewhat more strongly in women. The investigators speculate on mechanisms for the gender-specific effects of testosterone on diabetes risk (mostly via different effects on insulin

Continued

Differences of Endogenous Sex Hormones in Men and Women Linked to Type 2 Diabetes Risk

Continued

resistance). They also suggest sex hormone levels might be useful for predicting type 2 diabetes, albeit after additional studies to identify important levels for risk stratification. Study limitations included the use of observational data, lack of reliable data on free hormone levels, and the confounding effects of polycystic ovarian syndrome. Large prospective studies are needed to fully determine the predictive value of sex hormones in the development of type 2 diabetes.

Ding EL et al. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2006;295:1288-1299.

NDEI® upcoming CME events

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  - "The Cardiologist's Imperatives in Treating Patients With Diabetes." This activity brings together the best of emerging science and examines the clinical implication of anti-diabetic agents and their role in the management of CVD. Earn 2.5 *AMA PRA Category 1 Credits*™ –Free.

Clinical Insights® in Diabetes Post-Test April 2006

1. In an evaluation of the precision of the NCEP ATP-III definition of metabolic syndrome in identifying insulin-resistant individuals, what criterion had the greatest diagnostic accuracy? (Sierra-Johnson J et al. *Diabetes Care*. 2006;29:668-672.)
   a. High fasting-glucose levels
   b. Low HDL-C levels
   c. High waist circumference
   d. High triglyceride levels
2. In a study of the role of endogenous sex hormones in the development of type 2 diabetes in men and women, which of the following observations were made? (Ding EL et al. *JAMA*. 2006;295;1288-1299.)
   a. Testosterone levels were significantly *lower* in men with type 2 diabetes compared with men without diabetes.
   b. Testosterone levels were significantly *higher* in men with type 2 diabetes compared with men without diabetes.
   c. Testosterone levels were significantly *higher* in women with type 2 diabetes compared with women without diabetes.
   d. a and c

ANSWER KEY

1. c. *High waist circumference*. In this study, considering waist circumference alone as a quantitative trait improved diagnostic accuracy for insulin resistance better than any other metabolic syndrome component.
2. *d. a and c*. The nature of this contrasting relationship between the genders concerning androgen status and diabetes risk remains unclear.

For more information about upcoming NDEI CME and CE activities, visit us at www.ndei.org or call 1 (800) 606-6106. Visit www.ppscme.org for information on other CME or CE activities.

Clinical Insights® in Diabetes is co-edited by NDEI faculty members Mayer B. Davidson, MD, and Silvio E. Inzucchi, MD.

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NDEI MISSION STATEMENT

The *National Diabetes Education Initiative®* (NDEI®) is a multicomponent educational program on type 2 diabetes designed for endocrinologists, diabetologists, cardiologists, primary care physicians, and other healthcare professionals involved in the care and management of patients with type 2 diabetes and insulin resistance. NDEI programs address issues concerning insulin resistance and type 2 diabetes, from the epidemiology and pathophysiology of the disease and its associated complications to the therapeutic options for treatment and prevention.

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CME Activity Evaluation/Registration Form

Participants who wish to obtain CME credit for this activity, please complete the contact information below, sign this form, and fax it to (201) 430-1441. You may download previous issues of *Clinical Insights® in Diabetes* e-newsletters by visiting us online at www.ndei.org.

I completed this activity as designed: ______________________________
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Name: ______________________ **Address:** ______________________

City: ______________________ **State:** ____________ **Zip Code:** ____________

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Professional Classification: ☐ MD ☐ DO ☐ PharmD ☐ RN ☐ NP ☐ Other ______________________

Specialty: ☐ Endocrinology ☐ Cardiology ☐ Internal medicine ☐ Family medicine ☐ Other ______________________

Overall Program

1. The activity met the stated objectives in such a way that I am better able to:	Strongly Disagree		Disagree	Agree		Strongly Agree
a. Identify patients with type 2 diabetes and the metabolic syndrome	1	2	3	4	5	6
b. Select an appropriate therapeutic regimen for patients with type 2 diabetes and the metabolic syndrome	1	2	3	4	5	6

2. Overall, the activity was presented in a fair-balanced manner ☐ Yes ☐ No*

* If you checked "No," please explain. ______________________

____

3. In reflecting on your practice, what type of impact will this educational activity have?

☐ This program has validated my practice in the treatment of type 2 diabetes and its cardiovascular complications.

☐ Need more information before making a change.

(*Please specify what information you would require.*) ______________________

I will:

☐ Identify patients with type 2 diabetes and the metabolic syndrome

☐ Select an appropriate therapeutic regimen for patients with type 2 diabetes and the metabolic syndrome

☐ Other (*Please specify.*) ______________________

4. What topics should be dealt with in more detail? (*List topics*)

______________________ ______________________

______________________ ______________________

Thank you for your participation.