

# Urinary *myo*-Inositol-to-*chiro*-Inositol Ratios and Insulin Resistance

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Five papers have recently appeared dealing with urinary *myo*- and *chiro*-inositol excretion in diabetes in the Rhesus monkey and in humans, particularly as related to insulin resistance (1-5). Four papers (1,2,4,5) are in agreement, and a fifth (3) is in apparent disagreement. In the present report, we reevaluate the published data in the human studies and demonstrate overall agreement when 1) the ratio of increased urinary *myo*-inositol to decreased *chiro*-inositol is examined rather than only the urinary *chiro*-inositol excretion and 2) when the group of obese nondiabetic subjects studied by Ostlund et al. (3) is considered as potentially insulin resistant.

From the 40-year-old data obtained with a yeast growth analytical assay (6), as well as the most recent data obtained by gas chromatography/mass spec-

trometry (GC/MS) analysis, it is clear that urinary *myo*-inositol is increased in NIDDM and IDDM populations compared with control groups (1-5). One mechanism was shown to be a renal tubular competition between the carrier for glucose and *myo*-inositol (6). An additional mechanism to be considered on the basis of animal data presented in literature (7-9) is a defect in converting *myo*-inositol to *chiro*-inositol phospholipid. We (1,4) and others (5) have reported decreased urinary *chiro*-inositol excretion in NIDDM subjects, in NIDDM primates (2), and in the genetic nonobese Goto-Kakizaki model of NIDDM with severe insulin resistance (10). In three of these studies (2,4,5), the extent of decreased urine *chiro*-inositol has been directly correlated with the degree of insulin resistance. Thus, according to Ortmeyer et al.

(2), in the Rhesus monkey, insulin resistance measured by hyperinsulinemic euglycemic *M* values, glucose disappearance rates (*K* glucose), muscle needle-biopsy determinations of glycogen synthase activation state and of phosphorylase inactivation state, and adipose tissue biopsies of glycogen synthase activation state were directly correlated with urine *chiro*-inositol excretions (Figs. 1-4,6,7 in Ortmeyer et al. [2]). The correlations were especially striking at lower *chiro*-inositol excretion rates (Figs. 6,7 in Ortmeyer et al. [2]). In humans, studies in a limited number of control subjects, type II diabetic patients, and first-degree relatives (4) correlated the degree of insulin resistance determined by hyperinsulinemic euglycemic clamp *M* values with the urinary *chiro*-inositol excretion (Fig. 9 in Craig et al. [4]). Japanese type II diabetic subjects, patients with impaired glucose tolerance, and control subjects were studied with Bergman's minimal model technique (5). Insulin sensitivity index (*S*<sub>I</sub>) and glucose effectiveness (*S*<sub>G</sub>) were both directly correlated with urinary *chiro*-inositol excretions (Figs. 1,2 in Suzuki et al. [5]) in these three groups of subjects.

Accordingly, because *myo*-inositol excretion is clearly elevated and *chiro*-inositol is apparently decreased, we calculated ratios of urinary *myo*-inositol to *chiro*-inositol as a potentially more sensitive index of insulin resistance in the diabetic state (4) and one independent of units.

Table 1 presents the published data on urinary *myo*-inositol excretion from three laboratories determined for normal and obese nondiabetic subjects from mixed populations in the United States, including Native Americans and Japanese subjects (3-5). Mean values (4) and the median value (3) are in close agreement. Values in normal Pima Indians are somewhat higher, while the values in nondiabetic Japanese subjects are about twofold higher (5). Considering that diet was uncontrolled, this twofold range is not considered excessive.

Table 1 also presents analogous data on urinary *myo*-inositol excretion in NIDDM populations. As is clearly seen, in-

Table 1—GC/MS analysis of 24-h urine *myo*-inositol (μmol/day)

Group	Study		
	Craig et al. (4)	Ostlund et al. (3)	Suzuki et al. (5)
U.S.			
Normal	91 ± 11 (44)	—	—
NIDDM	270 ± 55 (50)	789 (35)	—
Obese nondiabetic	—	88 (42)	—
Pima			
Normal	112 ± 14 (20)	—	—
NIDDM	244 ± 90 (9)	—	—
Japanese			
Normal	—	—	192 ± 54 (10)
NIDDM	—	—	499 ± 112 (18)

Data are mean (*n*) or means ± SD (*n*). See the text for further discussion.

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GC/MS, gas chromatography/mass spectrometry.

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Table 2—GC/MS analysis of 24-h urine chiro-inositol ( $\mu\text{mol/day}$ )

Group	Study		
	Craig et al. (4)	Ostlund et al. (3)	Suzuki et al. (5)
U.S.			
Normal	36.1 $\pm$ 6.6 (44)	—	—
NIDDM	13.2 $\pm$ 3.6 (50)	12.4 (35)	—
Obese nondiabetic	—	2.4 (42)	—
Pima			
Normal	52.3 $\pm$ 10.6 (20)	—	—
NIDDM	11.1 $\pm$ 7.2 (9)	—	—
Japanese			
Normal	—	—	96.0 $\pm$ 17.6 (10)
NIDDM	—	—	32.3 $\pm$ 16 (18)

Data are mean (n) or means  $\pm$  SD (n). See the text for further discussion.

creased excretion is evident in all three studies (3–5), with the highest excretions observed in the report by Ostlund et al. (3).

Table 2 presents the urinary chiro-inositol excretion data in the same nondiabetic and diabetic populations in Table 1. With the exception of the extremely low medium value seen in the obese nondiabetic subjects (3), a two- to threefold variation is again observed in the nondiabetic subjects. This is not surprising when faced with uncontrolled diets.

Table 2 also presents the urinary chiro-inositol excretion data in the same NIDDM populations shown in Table 1. Again, about a threefold variation is seen, with the Japanese population having high values (5) and with excellent agreement in the NIDDM subjects in the two studies from the U.S. (3,4). In two of three reports

(4,5), decreased chiro-inositol is observed in NIDDM subjects compared with control subjects. In one case (3), increased excretion is seen when compared with the extremely low medium excretion value of obese nondiabetic subjects (Table 2).

In Table 3, the myo-inositol-to-chiro-inositol ratio data in control subjects, obese nondiabetic subjects, first-degree NIDDM relatives, and IDDM subjects is shown. Ratios of 2 to 2.5 are seen in the control subjects in two reports (4,5) in excellent agreement. Elevated ratios of 3.6 and 13.2 in glucose-intolerant Japanese subjects and in U.S. first-degree NIDDM relatives are shown. Further elevated ratios of 15.5, 20.5, 22.0, and 63.6 are seen in the four NIDDM subject groups, and ratios of 11 and 13.6 are seen in the IDDM subjects. The obese nondia-

betic subjects had an elevated ratio of 36.7.

As reported, this latter group has an increased BMI of  $29.5 \pm 8.1$  but a median plasma insulin value of  $64.4 \pm 48.1$  pmol/l, which is within the normal range. Thus, while the elevated urinary myo-inositol-to-chiro-inositol ratio suggests insulin resistance, the median plasma insulin value does not. Is it possible that the myo-inositol-to-chiro-inositol ratio is an earlier or perhaps more sensitive indicator of underlying insulin resistance than hyperinsulinemia? Further studies will be needed to define this point. In view of the present ratio results, it would appear prudent to consider the possibility that Ostlund et al.'s (3) population of obese nondiabetic subjects may not be free of underlying insulin resistance.

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Table 3—GC/MS analysis of 24-h urine myo-inositol-to-chiro-inositol ratios

Group	Study		
	Craig et al. (4)	Ostlund et al. (3)	Suzuki et al. (5)
U.S.			
Normal	91:36.1 = 2.5 (44)	—	—
NIDDM	270:13.2 = 20.5 (50)	789:12.4 = 63.6 (35)	—
IDDM	251:18.5 = 13.6 (35)	825:75 = 11.0 (13)	—
Obese nondiabetic	—	88:2.4 = 36.7 (42)	—
First-degree relative	90:6.8 = 13.2 (16)	—	—
Pima			
Normal	112:53.3 = 2.1 (20)	—	—
NIDDM	244:11.1 = 22.0 (9)	—	—
Japanese			
Normal	—	—	192:96 = 2.0 (10)
NIDDM	—	—	499:32.3 = 15.5 (18)
Impaired glucose tolerant	—	—	212:58.9 = 3.6 (8)

Data are ratio (n). See the text for further discussion.

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