8.84 ± 0.83 mM in IGT subjects, and 15.06 ± 3.67 mM in diabetic subjects. One-way analysis of variance was significant for each test ($P < 0.05$).

Figure 1*A* shows ROC curves when considering diabetic as disease present and IGT and nondiabetic as disease absent. AUC of FPG (0.944 ± 0.020) was not different from that of HbA_{1c} (0.935 ± 0.022), but that of fructosamine (0.856 ± 0.031) was significantly smaller than those of the other two ($P < 0.05$). Figure 1*B* shows ROC curves when regarding both IGT and diabetic as disease present and nondiabetic as disease absent. AUC of FPG (0.785 ± 0.016) was larger than that of HbA_{1c} (0.753 ± 0.026), although it was not statistically significant. AUC of fructosamine (0.706 ± 0.026) was significantly smaller than that of FPG ($P < 0.05$) but not of HbA_{1c}.

CONCLUSIONS

Our study sample included all subjects who visited a community hospital–based health checkup clinic during a given period. There was no influence of hypoglycemic therapy on the results because diabetic subjects treated with insulin or oral hypoglycemic agents were excluded from the analysis. Prevalence of diabetes and distributions of FPG, HbA_{1c}, and fructosamine at each glucose tolerance status in this study were consistent with other studies in Japan (7–9). Accordingly, the sample of this study is considered representative of the Japanese population.

The ROC analysis indicated that the discriminating ability of fructosamine was far inferior to both FPG and HbA_{1c}, thus the use of fructosamine as a screening test for diabetes is of no value. The diagnostic accuracy of HbA_{1c} for detecting diabetes, judged by the size of AUC, was almost the same as that of FPG, suggesting that HbA_{1c} is an alternative to FPG.

Another implication from this study is that the efficacy of all tests in detecting diabetes and IGT was considerably diminished compared with detection of diabetes alone. AUC of each test became smaller for diabetes and IGT than for diabetes alone, due to the considerable overlap between the test values of IGT and those of nondiabetic subjects. The efficacy in detecting IGT cases by these screening methods is inherently limited.

From the Department of Public Health, Tohoku University School of Medicine, Sendai, Miyagi, Japan.

Address correspondence and reprint requests to Ichiro Tsuji, MD, 6609 Copper Ridge Drive, T2, Baltimore, MD 21209.

Received for publication 18 September 1990 and accepted in revised form 13 March 1991.

ACKNOWLEDGMENTS

This study was supported in part by a Grant-in-Aid from the Ministry of Education, Japan (No. 02770281) and by the Japanese Association of Social Insurance (Zenkoku Shakai-hoken Rengou).

REFERENCES

1. Jovanovic L, Peterson CM: The clinical utility of glycosylated hemoglobin. *Am J Med* 70:331–38, 1981
2. Baker JR, O'Connor JP, Metcalf PA, Lawson MR, Johnson RN: Clinical usefulness of estimation of serum fructosamine concentration as a screening test for diabetes mellitus. *Br Med J* 287:863–67, 1983
3. Beck JR, Shultz EK: The use of relative operating characteristic (ROC) curves in test performance evaluation. *Arch Pathol Lab Med* 110:13–20, 1986
4. Hanley JA, McNeil BJ: The meaning and use of the areas under a receiver operating characteristic (ROC) curve. *Radiology* 143:29–36, 1982
5. Hanley JA, McNeil BJ: A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 148:839–43, 1983
6. World Health Organization: *WHO Expert Committee on Diabetes Mellitus: Second Report*. Geneva, World Health Org., 1980 (Tech. Rep. Ser., no. 646)
7. Kitazawa Y, Murakami K, Goto Y, Hamazaki S: Prevalence of diabetes mellitus detected by 75 g GTT in Tokyo. *Tohoku J Exp Med* 141 (Suppl.):229–34, 1983
8. Kiyose H, Tanaka G: Glucose tolerance screening method using a combination of fasting plasma glucose and hemoglobin A_{1c}. *J Jpn Diabetes Soc* 30:325–31, 1987
9. Ishii S, Iimura Y, Sakurabayashi I, Kawai T: Clinical significance of serum fructosamine measurement as a screening test for diabetes mellitus. *J Jpn Diabetes Soc* 31:217–22, 1988

Altering Triglyceride Concentrations Changes Insulin-Glucose Relationships in Hypertriglyceridemic Patients

Double-Blind Study With Gemfibrozil With Implications for Atherosclerosis

George Steiner, MD

Objective: To determine whether reducing triglyceride concentrations in humans reduces serum insulin levels and consider the implications of this for the insulin resistance of hypertriglyceridemia. Research Design and Methods: Insulin and glucose levels were determined during an oral glucose tolerance test (OGTT) in 14

volunteers who had a range of basal triglyceride levels. A double-blind crossover design was used to study active and placebo gemfibrozil and relate triglyceride changes to insulin and glucose levels. Diet and weight were kept constant. Results: Glucose concentrations during OGTT were the same in both treatment periods. Insulin concentrations were reduced in proportion to reductions in triglyceride. Conclusions: Triglyceride reduction in hypertriglyceridemic patients is associated with a decrease in serum insulin. This does not appear to be a direct effect of gemfibrozil, because it does not occur without a sufficient fall in triglyceride levels. Because glucose concentration remains the same despite the reduced insulin, the triglyceride reduction may result in greater sensitivity to insulin. Treatment of hypertriglyceridemia may break a vicious and potentially atherogenic cycle of hypertriglyceridemia and hyperinsulinemia. *Diabetes Care* 14:1077–81, 1991

There have been numerous suggestions of interrelationships between atherosclerosis and hyperinsulinemia (1–3), hypertriglyceridemia (4–8), and carbohydrate intolerance (9–11). These include a positive relationship between serum insulins and plasma triglycerides (TG) (12), an increase in the in vivo rate of very-low-density lipoprotein–TG production in the chronic hyperinsulinemic state (12–15); the presence of insulin resistance in hypertriglyceridemic patients, even in the absence of obesity, resulting in compensatory hyperinsulinemia (16). This hyperinsulinemia, in turn, could further aggravate hypertriglyceridemia, thereby perpetuating a vicious cycle that might have an atherogenic potential (17). Hence, it is important to learn whether this might break this cycle, thereby possibly correcting numerous risk factors for atherosclerosis.

RESEARCH DESIGN AND METHODS

Fourteen volunteers with basal plasma triglycerides from 1.6 to 18.3 mM and no disorder, diet, or drug known to affect lipoprotein or glucose levels or change insulin sensitivity were studied during three 8-wk periods (placebo washout and 2 treatment periods). During the treatment periods, each was assigned in a double-blinded crossover manner to either gemfibrozil (600 mg twice daily) versus placebo. Lipoproteins were evaluated at the end of each period. Also at the end of each treatment period, a 75-g oral glucose tolerance test (OGTT; 18) sampling for glucose and insulin determinations was performed. After each 8-wk period, body weight was measured, adherence to a weight-maintaining balanced diet was ascertained by dietary interview and evaluation of a 3-day food record, and drug compliance (94–100%) was assessed by pill counting.

Ultracentrifugation (19) and/or isoelectric focusing (20) was used to exclude anyone with chylomicronemia, an accumulation of intermediate-density lipoprotein, or an apolipoprotein E2:2 phenotype. TG and cholesterol concentrations were measured enzymatically (triglyceride kit no. 297771, cholesterol kit no. 237574, Boehringer Mannheim, Mannheim, Germany), plasma glucose with a Glucose Analyzer II (Beckman, Fullerton, CA), and serum insulin concentrations with the method of Starr et al. (21). Statistical analyses used programs designed by Glantz (22).

TABLE 1
Relationship between changes in triglyceride levels and responses to oral glucose tolerance tests (OGTTs)

	Poor responders			Good responders			
	Placebo	Gemfibrozil	Paired difference	Placebo	Gemfibrozil	Paired difference	*P**
Triglyceride (mM)	2.62 ± 0.32	1.70 ± 0.48	−0.93 ± 0.22†	6.65 ± 1.59	1.95 ± 0.39	−4.70 ± 1.50‡	<.02
OGTT (at 60 min)							
Glucose (mM)	8.8 ± 1.2	9.9 ± 0.7	+1.1 ± 0.8§	9.1 ± 1.1	10.0 ± 1.2	+0.9 ± 0.8‖	NS
IRI (pM)	412 ± 68	506 ± 92	+94 ± 85§	864 ± 138	573 ± 111	−292 ± 98‡	<.01
OGTT (0–180 min)							
Glucose (mM)	35.5 ± 3.6	36.0 ± 6.1	+0.5 ± 7.1§	36.4 ± 3.9	39.4 ± 5.2	+3.0 ± 1.9‖	NS
IRI (pM)	1275 ± 223	1311 ± 294	36 ± 201§	2790 ± 357	2015 ± 336	−774 ± 222‡	<.01

Changes in plasma triglyceride concentrations were compared to changes in glucose and insulin responses measured at 60 min or summed from 0 to 180 min after 75-g oral glucose load. Individuals who showed poor triglyceride response to gemfibrozil were compared with those who showed good response. Data are means ± SE. Differences between each individual's parameters on placebo were subtracted from those on gemfibrozil, and mean ± SE for these differences is shown. Magnitude of differences in good vs. poor responders was compared by calculating *P* between group means with Student's *t* test. IRI, immunoreactive insulin.

*P, good responders vs. poor responders for both gemfibrozil and placebo.

†$P < 0.01$, ‡$P < 0.01$ gemfibrozil vs. placebo in poor responders and good responders, respectively.

§‖, NS.

RESULTS

The 14 volunteers (12 men, 2 women) had a mean ± SE age of 54.6 ± 4.7 yr. They were not grossly obese (body mass index 26.5 ± 0.8 kg/m^2). The fasting glucose of one subject was 7.9 mM, whereas that of the rest was ≤6 mM. Mean ± SE fasting cholesterol level was 6.25 ± 0.37 mM (range 4.7–9.8 mM), and fasting TG level was 4.71 ± 1.10 mM (range 1.6–18.3 mM).

Fasting plasma TG concentrations of the entire group of volunteers were plotted against the insulin concentrations. This was done initially only for those determinations conducted while the participants were on placebo. The data resembled that reported previously (12). There was little relationship between fasting insulin and fasting TG concentrations (r = 0.113). However, there was a positive correlation between the fasting plasma TG concentration and the insulin concentrations either at 60 min after the glucose challenge (immunoreactive insulin [IRI], 94.4TG + 266, r = 0.681) or summed from 0 to 180 min (IRI = 175.9 TG + 1309, r = 0.504). There was no significant change in these relationships when data were included from OGTTs conducted while participants were taking gemfibrozil (at 60 min, IRI = 70TG + 384, r = 0.662; sum of all insulins, IRI = 148TG + 1436, r = 0.455). The failure of gemfibrozil to alter these relationships suggested that the drug itself might not exert a direct effect on serum insulin, but that it might do so by altering the concentration of plasma TG.

To examine the effects of the magnitude of TG reduction in greater detail, the data were examined in those in whom gemfibrozil produced a TG decrease >1.7 mM, good responders versus those in whom the decrease was <1.7 mM (poor responders). The fasting TG concentration in the eight good responders ranged from 3.2 to 18.3 mM. In the six poor responders, it ranged from 1.6 to 4.4 mM. Three of six poor responders had TG concentrations >95th percentile for their age and sex. The OGTT glucose concentrations were not significantly different between these two categories of volunteers (Table 1; Fig. 1). In those who, despite good adherence to the drug, showed only a small change in plasma triglyceride, there was no difference in insulin or glucose levels during the OGTTs conducted on either placebo or active drug. By contrast, in those volunteers who showed a good TG reduction, insulin levels during the OGTTs were lower while on active gemfibrozil (Table 1). The change in the insulin levels in each individual was positively correlated (r = 0.59) with the gemfibrozil-induced change in his/her plasma TG concentration (Fig. 2).

These observations could not be attributed to differ-

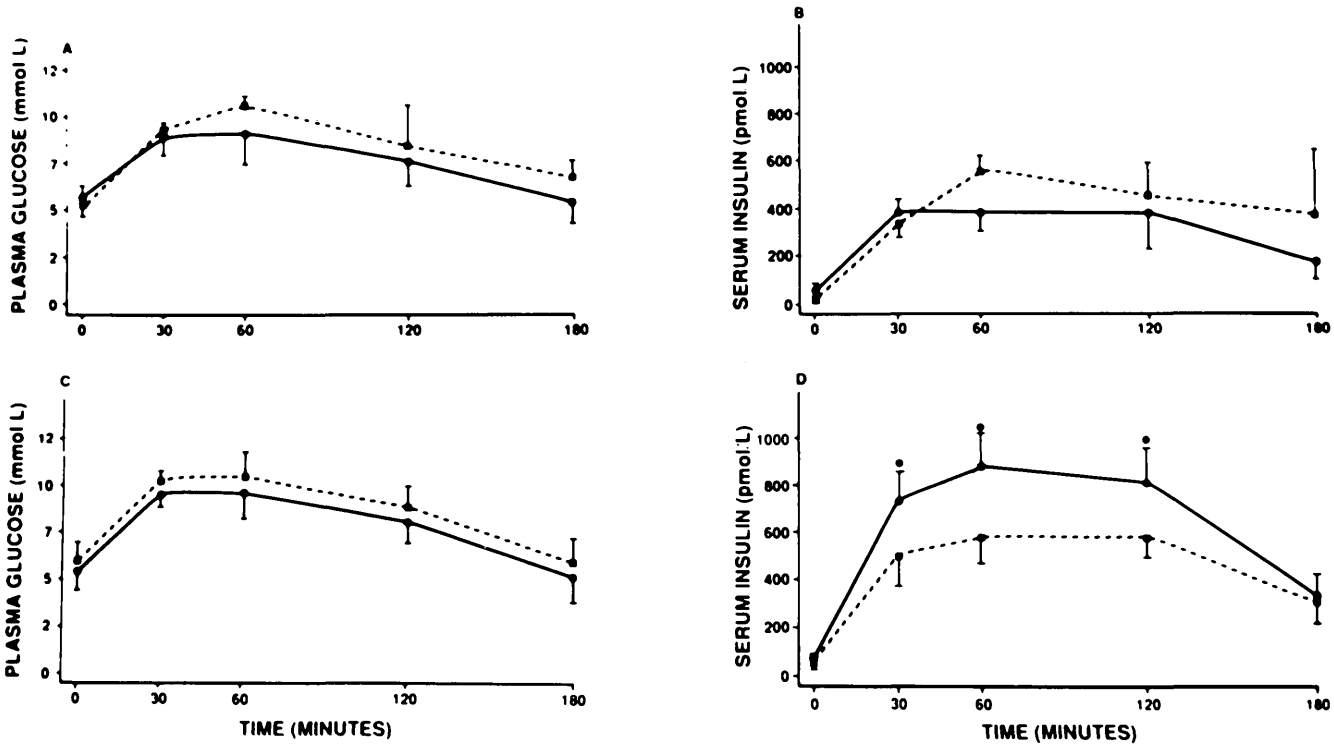

FIG. 1. Glucose and insulin concentrations during oral glucose tolerance tests on placebo (*solid lines*) and gemfibrozil (*dashed lines*) in those who showed substantial decrease of fasting triglyceride (*C* and *D*) compared with those who showed minimal change of triglyceride (*A* and *B*). Values are means ± SE. *$P < 0.005$, placebo vs. active drug at same time.

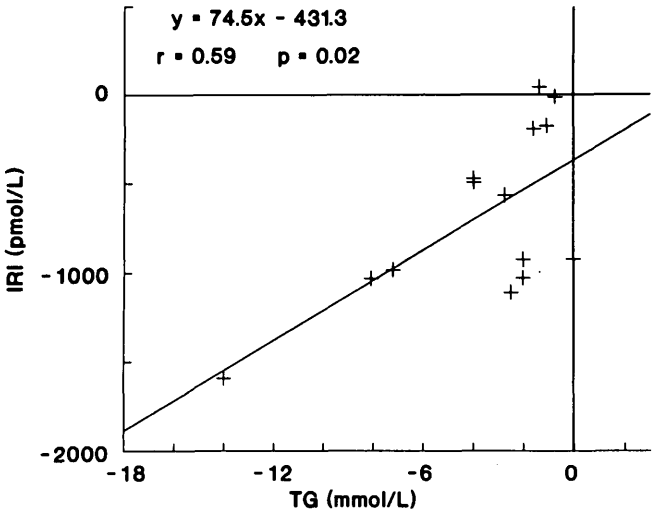

FIG. 2. Gemfibrozil-induced change in each individual's plasma triglyceride compared with change in sum of his/her insulin levels measured between 0 and 180 min during oral glucose tolerance tests in Fig. 1. IRI, immunoreactive insulin; TG, triglyceride.

ences in a subject's weight or diet, because they did not change in any individual between the gemfibrozil and placebo periods.

CONCLUSIONS

We have observed previously that hypertriglyceridemic individuals, even if lean, are resistant to the effects of insulin on glucose utilization and in an attempt to compensate may develop hyperinsulinemia after a glucose challenge (16). This study was undertaken to determine whether such insulin levels would change as a consequence of changes in plasma TG concentrations. We elected not to alter plasma TG levels by dietary methods, because the diet itself or any weight changes might affect insulin sensitivity. Therefore, gemfibrozil was used.

Similar plasma glucose levels were obtained in the OGTTs done on subjects taking gemfibrozil or placebo GTTs (Table 1; Fig. 1). Also, in those in whom gemfibrozil produced only a small reduction in TG, there was no difference in the insulin levels in subjects taking gemfibrozil versus placebo. However, when the active drug produced a larger decrease in TG levels, insulin levels were reduced. Because drug adherence was good in all volunteers (>94%), and there was no difference in insulin levels on active drug versus placebo unless there was a larger decrease in TG concentration, gemfibrozil alone did not appear to have a direct effect on insulin. In fact, the magnitude of reduction in insulin levels during the OGTT was directly proportional to the magnitude of reduction of plasma TG (Fig. 2).

The reduction in insulin levels could have reflected either a decreased responsiveness of the pancreatic β-cell, an increase in the body's sensitivity to insulin, or both. If the first of these possibilities were the case, the plasma glucose levels during the active drug period should have been higher than on placebo. Therefore, I postulate that the individual's sensitivity to insulin increased. During the gemfibrozil period, there was no change in either weight or diet. Hence, these two factors could not account for the improvement in sensitivity to insulin. This suggests that the increase in sensitivity to insulin was associated with the reduction of plasma TGs.

Clofibrate and bezafibrate, which are related drugs, have been studied in diabetic individuals (23–27). Because of the greater impairment of pancreatic function and the greater resistance to insulin that may exist in people with diabetes, it was more probable that differences in insulin levels, and possibly sensitivity, would be seen in our patients. Previous studies did not examine the relationship of their changes to the magnitude of the drug-induced differences in triglycerides, and some studies did not control for weight and diet. One study that examined insulin sensitivity failed to find any effect of bezafibrate (27). However, only 3 of 10 patients had a reduction of plasma TG concentration >1.7 mM, a change that the current study suggests might have been too little to alter insulin sensitivity.

Although there may be other unrecognized factors, these data are consistent with the hypothesis that the insulin resistance of hypertriglyceridemic individuals is attributable to their hypertriglyceridemia. It has been postulated previously that hypertriglyceridemia, insulin resistance, and hyperinsulinemia may be related in a vicious cycle that could carry an atherogenic potential (17). This study did not attempt to suggest at what point this cycle starts. However, it indicated that the cycle may be interrupted by reducing plasma TG. This could remove several potential atherogenic risk factors, e.g., hypertriglyceridemia (4–6), carbohydrate intolerance (7–9), and hyperinsulinemia (1–3).

From the Division of Endocrinology and Metabolism, Toronto General Division of The Toronto Hospital, and Department of Medicine, University of Toronto, Toronto, Ontario, Canada.

Address correspondence and reprint requests to Dr. George Steiner, Room 11N-225, Eaton Wing, Toronto General Division of The Toronto Hospital, 200 Elizabeth Street, Toronto, Ontario, Canada M5G 2C4.

Received for publication 27 August 1990 and accepted in revised form 13 May 1991.

ACKNOWLEDGMENTS

This study was funded by the Canadian Diabetes Association.

I express gratitude to the staff of the Lipid and Atherosclerosis Laboratory at the Toronto General Hospital for technical assistance in the assays, K. Mackie for having monitored the volunteers, the volunteers for their time and effort, and Dr. M. Kopaniak for invaluable advice.

REFERENCES

1. Welborn TA, Wearne K: Coronary heart disease incidence and cardiovascular mortality in Busselton with reference

to glucose and insulin concentrations. *Diabetes Care* 2:154–60, 1979
2. Pyörälä K: Relationship of glucose tolerance and plasma insulin to the incidence of coronary heart disease: results from two population studies in Finland. *Diabetes Care* 2:131–41, 1979
3. Ducimitiere P, Eschwege L, Papoz PL, Claude RJR, Rosselin G: Relationship of plasma insulin levels to the incidence of myocardial infarction and coronary heart disease mortality in a middle-aged population. *Diabetologia* 19:205–10, 1980
4. Steiner G, Schwartz L, Shumak S, Poapst M: The association of increased levels of intermediate density lipoproteins with smoking and with coronary artery disease. *Circulation* 75:124–30, 1987
5. Bottiger LE, Carlson LA: Risk factors for ischaemic vascular death for men in the Stockholm Prospective Study. *Atherosclerosis* 36:389–408, 1980
6. Aberg H, Lithell H, Selinus I, Hedstrand H: Serum triglycerides are a risk factor for myocardial infarction but not for angina pectoralis. *Atherosclerosis* 54:89–97, 1985
7. Castelli WP: The triglyceride issue: a view from Framingham. *Am Heart J* 112:432–37, 1986
8. Austin MA: Plasma triglyceride as a risk factor for coronary heart disease: the epidemiologic evidence and beyond. *Am J Epidemiol* 129:249–59, 1989
9. Steiner G: Atherosclerosis, the major complication of diabetes. In *Comparison of Type I and Type II Diabetes*. Vranic M, Hollenberg CH, Steiner G, Eds. New York, Plenum, 1985, p. 277–97
10. Fuller JH, McCartney P, Jarrett RJ, Keen H, Rose G, Shipley MJ, Hamilton PJS: Hyperglycemia and coronary heart disease: the Whitehall study. *J Chronic Dis* 32:721–28, 1979
11. Stamler R, Stamler J (Eds): Asymptomatic hyperglycemia and coronary heart disease, a series of papers by the International Collaborative Group based on studies in fifteen populations. *J Chronic Dis* 32:683–837, 1979
12. Olefksy JM, Farquhar JW, Reaven GM: Reappraisal of the role of insulin in hypertriglyceridemia. *Am J Med* 57:551–60, 1974
13. Streja DA, Marlis EB, Steiner G: The effects of prolonged fasting on plasma triglyceride kinetics in man. *Metabolism* 26:505–16, 1977
14. Kazumi T, Vranic M, Steiner G: Triglyceride kinetics: effects of dietary glucose, sucrose of fructose alone or with hyperinsulinemia. *Am J Physiol* 250:E325–30, 1986
15. Steiner G, Haynes FJ, Yoshino G, Vranic M: Hyperinsulinemia and in vivo very low density lipoprotein-triglyceride kinetics. *Am J Physiol* 246:E187–92, 1984
16. Steiner G, Morita S, Vranic M: Resistance to insulin but not to glucagon in lean human hypertriglyceridemics. *Diabetes* 29:899–905, 1980
17. Steiner G, Vranic M: Insulin and hypertriglyceridemia: a vicious cycle with atherosclerotic potential. *Int J Obes* 6 (Suppl. 1):117–24, 1982
18. West K: Diagnosis of diabetes mellitus. In *Diabetes Mellitus*. Vol. 5. Rifkin H, Raskin P, Eds. Bowie, MD, Brady, 1982, p. 103–108
19. Reardon MF, Poapst ME, Steiner G: The independent synthesis of intermediate density lipoproteins in type III hyperlipoproteinemia. *Metabolism* 31:421–27, 1982
20. Rall SC Jr, Weisgraber KH, Mahley RW: Isolation and characterization of apolipoprotein E. *Methods Enzymol* 128:273–87, 1986
21. Starr JR, Horwitz DL, Rubenstein AH, Mako ME: *Methods of Hormone Radioimmunoassay*. 2nd ed. New York, Academic, 1979, p. 613–42
22. Glantz SA: *Primer of Biostatistics*. 2nd ed. New York, McGraw-Hill, 1987
23. Galvet GD, Blight L, Franklin J, Oliver J, Wise P, Gallus AS: The effects of clofibrate on plasma glucose, lipoproteins, fibrinogen, and other biochemical and heamatological variables in patients with nature onset diabetes mellitus. *Eur J Clin Pharmacol* 17:355–62, 1980
24. Schade DS, Eaton RP, George S, Conway M, Kminsky N, Sivinski J: Metabolic effects of clofibrate in insulin-dependent ketosis-prone diabetic man. *Metabolism* 27:461–68, 1978
25. Ferrari C, Testori GP, Bertazzoni A, Romussi M, Caldara R, Frezzati S: Increased glucose disappearance rate after short-term clofibrate administration in normal subjects and patients with chemical diabetes. *Horm Metab Res* 10:4–6, 1978
26. Ratzmann M-L, Rjasanbowski I, Bruns W, Ratzmann KP: Effects of clofibrate therapy on glucose tolerance, insulin secretion and serum lipids in subjects with hyperlipoproteinemia and impaired glucose tolerance. *Exp Clin Endocrinol* 82:216–21, 1983
27. Riccardi G, Genovese S, Saldalamacchia G, Patti L, Marotta G, Postiglione A, Rivellese A, Capaldo B, Mancini M: Effects of bezafibrate on insulin secretion and peripheral insulin sensitivity in hyperlipidemic patients with and without diabetes. *Atherosclerosis* 75:175–81, 1989

Relationship Between Cows' Milk Consumption and Incidence of IDDM in Childhood

Knut Dahl-Jørgensen, MD
Geir Joner, MD
Kristian F. Hanssen, MD

Objective: To compare age-standardized incidence rates of diabetes in children 0–14 yr of age and cows' milk consumption in various countries. Research Design and Methods: Ecological correlation study. Only incidence rates from diabetes registries carefully validated by the Diabetes Epidemiology Research International Study Group were used—Finland, Sweden, Norway, Great Britain, Denmark, United States, New Zealand, Netherlands, Canada, France, Israel, and Japan. Data on fluid cows' milk consumption in corresponding countries were obtained from the International Dairy Federation. Results: Correlation between milk