Hyperketonemia Induced in Man by Medium-chain Triglyceride

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SUMMARY

The effect of a medium chain triglyceride (MCT) preparation on blood ketones was determined in fourteen normal subjects and six patients with diabetes mellitus of the maturity-onset type. Ingestion of 100 gm. of the MCT (containing 86 per cent C_8 and 14 per cent C_{10} fatty acids) was followed by a small but statistically significant rise in blood ketones in each of the groups. The rise in ketones was slightly but significantly higher in the diabetic patients than in the normal subjects. In all subjects, ketone rises were negligible after ingestion of 100 gm. of corn oil.

The ketogenic effect of MCT may result in part from its rapid absorption from the gut, with a high proportion of the component fatty acids traveling in the portal vein directly to the liver in the free acid form. In the liver, these fatty acids appear to be rapidly degraded and converted in part to ketones. The predictable mild hyperketonemia induced by MCT makes this glyceride a useful tool in the study of ketogenesis. DIABETES *15*:723-25, October, 1966.

In 1959 Schön, Gelpke, and Lippach[1] fed a specially prepared triglyceride, containing fatty acids ranging in chain length from C_8 to C_{12}, to a group of human subjects and observed a rise in blood and urine concentrations of acetone and β-hydroxybutyric acid. When a similar quantity of long chain triglyceride (margarine) was administered to the same subjects, changes in blood and urine ketones were negligible. In the present studies the observations of Schön et al. have been confirmed and extended. The effect on blood ketones of a medium chain triglyceride (MCT) preparation has been compared with that of corn oil in fourteen healthy adult subjects and six patients with maturity-onset diabetes mellitus.

MATERIALS AND METHODS

One-hundred grams of fat (MCT or corn oil), 31 gm. of casein and 47.3 gm. of dextrose were homogenized in sufficient water to provide 250 ml. of a liquid formula emulsion. This quantity was consumed by each subject over a three- to five-minute period. All subjects were in the postabsorptive state prior to administration of formula. The fatty acids in the MCT preparation were 86 per cent caprylate (C_8) and 14 per cent caprate (C_{10}). The corn oil contained no fatty acids of carbon chain length less than 14. Venous blood ketones and glucose were measured at 0, ½, 1, 1½, 2 and 3 hr. after the test meal. Blood ketone concentration was determined by a modification of the method of Michaels et al.[2] and blood glucose by the Nelson-Somogyi procedure.[3] Except for the six patients with maturity-onset diabetes mellitus, all subjects were free of hepatic, gastrointestinal and metabolic disease. The diabetic patients, two men and four women, ranged in age from forty-six to seventy-two years and were controlled by diet alone. Only one of these patients, a forty-nine-year-old Negro woman, was obese. Ten subjects received MCT first, and ten were given corn oil as the initial fat. An interval of at least two days separated the ingestion of the two test meals.

RESULTS

In the normal subjects there was a rise in blood glucose concentration after each test meal, ranging from 20 to 40 mg. per 100 ml., with a peak reached at one-half to one hour and a subsequent return to baseline by two to three hours. In the three diabetic patients in whom glucose responses were measured following each test meal, the blood sugar values started from a higher baseline and reached somewhat higher levels at two hours than the nondiabetic subjects, with a return to control values by three hours. The nature of the fat in the test meal did not influence the blood glucose response.

Following MCT administration all fourteen nondiabetic subjects showed an increase in blood ketones averaging 6.2 ± 0.6 mg. per 100 ml. (All means are

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given together with their standard deviations.) Baseline ketone values averaged 2.4 ± 0.1 mg. per 100 ml. before corn oil was administered and 1.9 ± 0.1 mg. per 100 ml. before MCT was given. The increment was statistically significant ($p < 0.01$). Maximum ketone increases usually occurred at 30 to 120 min. After corn oil, the same group exhibited a mean maximal rise in blood ketones of 1.7 ± 0.17 mg. per 100 ml.

In the six diabetic subjects a mean increase in blood ketones of 9.7 ± 0.4 mg. per 100 ml. followed MCT ingestion, while corn oil induced a mean maximal rise of 1.8 ± 0.4 mg. per 100 ml. The mean rise in ketones of the diabetic group was significantly greater than that of the nondiabetic subjects ($p < 0.01$). Initial values in the diabetic group averaged 3.2 ± 0.2 mg. per 100 ml. before corn oil was administered and 2.6 ± 0.4 before the MCT was given. In general, the MCT formula was well tolerated; however, one subject complained of abdominal pain soon after ingestion of the formula, and one had diarrhea the following day.

DISCUSSION

In 1917 Embden et al.[4,5] perfused the canine liver with caprylic acid and observed a prompt rise in hepatic output of acetoacetate. More recently, Werk and associates[5] were able to demonstrate a fivefold increase in splanchnic ketone production following sodium caprylate infusion into normal human subjects. Hashim et al.[6] showed in the dog that when an MCT preparation consisting entirely of C_8 fatty acids was directly instilled into the duodenum this triglyceride was readily hydrolyzed, with its component fatty acids rapidly absorbed into the portal venous system where they traveled to the liver as free fatty acids (FFA). This, and other studies,[7] indicate that most of the medium chain acids from MCT probably enter the portal vein as FFA and travel directly to the liver. Thus, in a sense, ingestion of MCT results in hepatic perfusion by C_8 and C_{10} fatty acids, a situation somewhat analogous to that occurring in the experiments of Embden et al.[4] and Werk and associates.[5]

There is evidence that fatty acids of chain length C_{12} and below are more likely to be metabolized within the liver than to form esters or be lengthened.[8,9] Thus, perfusion of the liver with caprylate would be expected to result in a more rapid production of acetyl coenzyme A fragments, perhaps in excess of the ability of the tricarboxylic cycle to accommodate them. Such a metabolic situation would favor the formation of acetoacetate and the other "ketones" that derive from it. Moreover, there is some evidence to suggest that the terminal CH_3CO- units derived from fatty acids are more likely to participate in ketogenesis than the intermediate $-CH_2CO-$ units.[10,11] Since the C_8 and C_{10} acids of MCT are more readily oxidized than longer chain acids,[10] and since they contain a higher proportion of such terminal "acetylating" units in relation to the total number of available C_2 fragments, the relatively abundant presence in the liver of these fragments might favor ketone body production on these bases. Finally, the studies of Wieland et al.[12] have suggested that perfusion of the liver by caprylate may inhibit the velocity of the tricarboxylic acid (TCA) cycle by altering the redox potential of cytoplasmic DPN. Such suppression of the TCA cycle would promote ketogenesis.[13]

Although the MCT-induced rise in blood ketones is statistically highly significant, the degree of hyperketonemia achieved with this rather large quantity of glyceride is not great. Levels of hyperketonemia of 15 to 25 mg. per 100 ml. are readily achieved by prolonged fasting or a low carbohydrate, high fat diet, and patients in diabetic acidosis reportedly have exhibited blood ketone levels ranging above 100 mg. per 100 ml.[14] Nevertheless, by means of MCT administration it is possible to induce a predictable mild hyperketonemia in normal individuals and this characteristic of the glyceride may make it useful in the study of mechanisms of ketogenesis. Preliminary observations in six diabetic patients of the maturity-onset type suggest that such individuals show a significantly greater ketonemic response to MCT than normal subjects. In terms of clinical significance, however, the difference is modest.

It is noteworthy that in all of the subjects, hyperketonemia occurred despite the concurrent administration of glucose, resulting in significant rise in blood sugar. This observation is consistent with earlier reports[9] indicating that in rats administered caprylate is almost completely oxidized within a few hours, even if the animals are in the fed state.

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Total Body Fat and Skinfold Thickness in Children

While the estimation of total body fat of intact individuals can be done by hydrostatic weighings, taking into account the residual air, such procedures are usually too cumbersome for routine use in determination of total body fat. The correlation between total body fat and the measurement of the thickness of skinfolds determined in various parts of the body has been discussed earlier (*Nutrition Reviews* *14*:289, 1956).

The relationships between skinfold thickness and body density from which the total fat value is obtained using empirical equations, varies according to sex and the age of the group studied. Recently, J. Parizkova (*Metabolism* *10*:194, 1961) carried out studies in which he determined the relationship between body density and skinfold thicknesses in groups of children between nine and sixteen years of age. He used two groups of boys, one consisting of sixty-six boys from nine to twelve years and the other fifty-seven boys between thirteen and sixteen. He also used two groups of girls, a younger group of fifty-six girls from nine to twelve and an older group of sixty-two girls.

According to the common clinical criteria, all children were healthy. Data presented consisted of the relationship between body density and the sum of the skinfold thicknesses obtained in ten different sites for all four groups. Nomograms were also presented for each of the sexes and each of the two age groups; the per cent body fat or body density was correlated with measurement of the skinfold thickness at two sites, on the back of the arm and underneath the scapula. These studies allow the extension of the use of the skinfold thickness procedure to both males and females from nine to sixteen years old, thus expanding the range of usefulness of this type of measurement.

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