COMMENTARY

Differences in Fat, Carbohydrate, and Protein Metabolism between Lean and Obese Subjects Undergoing Total Starvation

M. Elia, R.J. Stubbs,† and C.J.K. Henry‡*

Abstract

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Despite extensive experimental studies on total starvation, many of the findings relating to protein, fat (plus ketone body), and carbohydrate metabolism remain confusing, although they become more consistent when considered in relation to the degree of initial obesity. During prolonged starvation, protein loss and percent energy derived from protein oxidation are 2- to 3-fold less in the obese than in the lean; percent urine N excreted as urea is 2-fold less in the obese; and the contribution of protein to net glucose production is only about half in the obese compared to lean subjects. During short-term starvation (first few days) the following differences are reported: hyperketonaemia is typically 2-fold greater in lean subjects, but associated with a 2-fold lower uptake of ketone bodies by forearm muscle; glucose tolerance becomes impaired more in lean subjects; and both protein turnover and leucine oxidation increase in the lean, but may show no significant change in the obese. It is no longer acceptable to describe the metabolic response to starvation as a single typical response. The differences between lean and obese subjects have important physiological implications, some of which are of obvious relevance to survival.

Key words: human, starvation, protein, carbohydrate, fat, ketone bodies

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From *Addenbrooke's Hospital, Box 133, Hills Road, Cambridge CB2 2QQ; †Rowett Research Institute–Human Nutrition Unit, Bucksburn, Aberdeen AB2 9SB; and ‡School of Biological and Molecular Sciences, Oxford Brookes University, Oxford OX3 0BP.
Address correspondence to M. Elia, Addenbrooke's Hospital, Box 133, Hills Road, Cambridge CB2 2QQ.

Introduction

In the 1960s and 1970s, a series of studies on protein–energy metabolism and net inter-organ flux of substrates were undertaken to establish the metabolic response of obese subjects to prolonged total starvation (no energy intake for up to 6 weeks) (1). Although the results of such studies have been incorporated into standard texts of biochemistry and nutrition, they do not reflect the spectrum of metabolic responses, which are influenced by age, sex, and adiposity. About a century ago it was already known that the proportion of energy derived from protein oxidation during starvation was less in mammalian and avian species with a large percent body fat (e.g., pig, goose) than those with lower percent body fat (e.g., rodents, dogs, lean chicken) (2,3). Since then, two further concepts have developed: an extension of the concept about the effect of adiposity on protein economy during starvation to animals within the same species, including humans; and the idea that the degree of adiposity has important effects on the metabolic response to starvation. Sufficient information has now accumulated from disparate forms of research that it is appropriate to summarize some of the effects of increasing adiposity on the metabolic responses to total starvation (no energy intake) in humans and to consider the physiological significance of these responses.

Protein Metabolism

Although obese individuals have more body protein and fat-free tissue than lean individuals (up to ~50% more), they lose these components at a slower rate during prolonged starvation than lean individuals (3). Furthermore, the proportion of energy derived from protein oxidation decreases with time in obese individuals (3,4) (Figure 1) but shows little sign of a reduction in lean individuals undergoing total starvation for up to a month. The effect of initial body mass index and percent body fat on the proportion of energy derived from protein oxidation during starvation (>2 weeks duration) is shown in Figure 2.

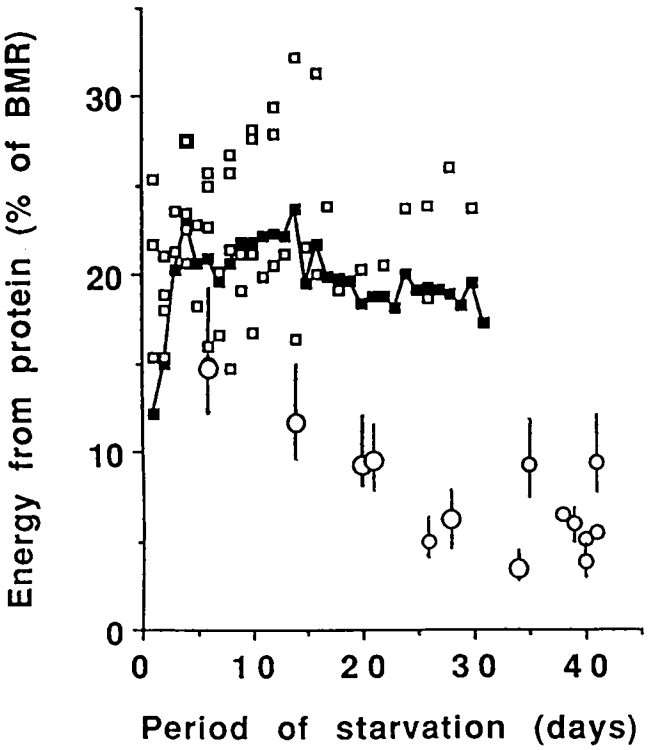

Figure 1: Effect of length of total starvation on the percent contribution of protein oxidation to basal metabolic rate (BMR) in lean subjects [solid squares (5) – open squares (3,6,7)], and obese subjects (large circles from groups of individuals and small circles from individual subjects). Based on Elia, 1992 (3).

It might seem paradoxical that obese individuals, who have more body protein, should spare it to a greater extent than lean individuals, but the responses in both lean and obese subjects can be regarded as adaptive (Table 1). Although starvation studies in genetically obese Zucker rats suggest that some fat may be retained at the time of death (in contrast to lean rats, which use virtually all their fat), the majority of the fat is lost (at least 82%) (9). Excess fat can act as an energy reservoir and prolong survival time, provided sufficient lean tissue remains to perform vital body functions. A much greater reduction in protein oxidation in the obese would also be required to ensure prolonged survival. In contrast, a greater proportion of energy derived from protein oxidation would be expected in lean individuals, and this is supported by experimental observations (Figures 1 and 2) (3,4). However, the mechanisms by which lean and fat tissue losses are co-ordinated are largely unknown. This is partly because information on intermediary metabolism and circulating concentration of substrates, hormones, and growth factors in lean subjects undergoing prolonged total starvation is lacking.

The decrease in protein oxidation in obese subjects undergoing prolonged starvation is associated with a several-fold reduction in urine urea excretion and a reduction in the proportion of N excreted as urea (10). In contrast, there is a several-fold increase in the excretion of urinary ammonia (Figure 3), which occurs as a physiological response to mild metabolic acidosis (the hyperketonaemia of starvation). The significance of this to glucose metabolism in lean and obese subjects is discussed below under "carbohydrate metabolism."

The amount of urea excreted in urine does not accurately reflect the amount of urea produced in the liver, partly because a proportion of the urea [reported to be ~20–25% (14) in normal subjects (6) but as much as 40% in some studies (15)] is hydrolysed to ammonia and water by bacteria, which are mainly present in the large bowel. The ammonia may be used not only to reform urea (ammonia-urea recycling), but also to synthesise many amino acids. Therefore, it has been proposed that recycling of urea N increases the effective "N intake" and may improve protein economy in some circumstances. A recent study (16) suggests that the main predictor of the variability in urea production and hydrolysis in women (urea recycling) is the amount of body fat. If such differences can be confirmed and shown to operate during starvation, they could help explain some of the differences in protein economy, discussed above. Parenthetically, urea hydrolysis has been considered to occur as a result of juxta-mucosal bacterial metabolism, and to be active during parenteral nutrition in adults (17) and neonates, even in those that have received no oral intake from birth (18). However, there is no information about differences in urea recycling between lean and obese individuals during prolonged starvation, or about the mechanisms that might relate urea kinetics to adipose tissue mass.

No significant differences have been demonstrated between lean and obese subjects in net protein oxidation (and proportion of energy derived from protein oxidation) when calculated from the rate of net N excretion (with or without indirect calorimetry) during the first few days of starvation (3). However, studies undertaken by tracer methods suggest that some differences exist as early as 60 hours of starvation. For example, Umpleby et al. (19) (Table 2) suggest that in lean subjects there is a 230% increase in leucine oxidation (12 hours vs. 60 hours of starvation), whereas in obese subjects there is a small non-significant increase (17%). Furthermore, the rate of leucine appearance increased significantly by a little more than 50% in lean subjects, but it decreased (17%) in the obese. Again, the mechanisms responsible for these differences are unclear.

Fat and Ketone Body Metabolism

Fat becomes the major source of energy during starvation accounting for ~94% of the energy expenditure in obese subjects and 78% in lean subjects (with protein

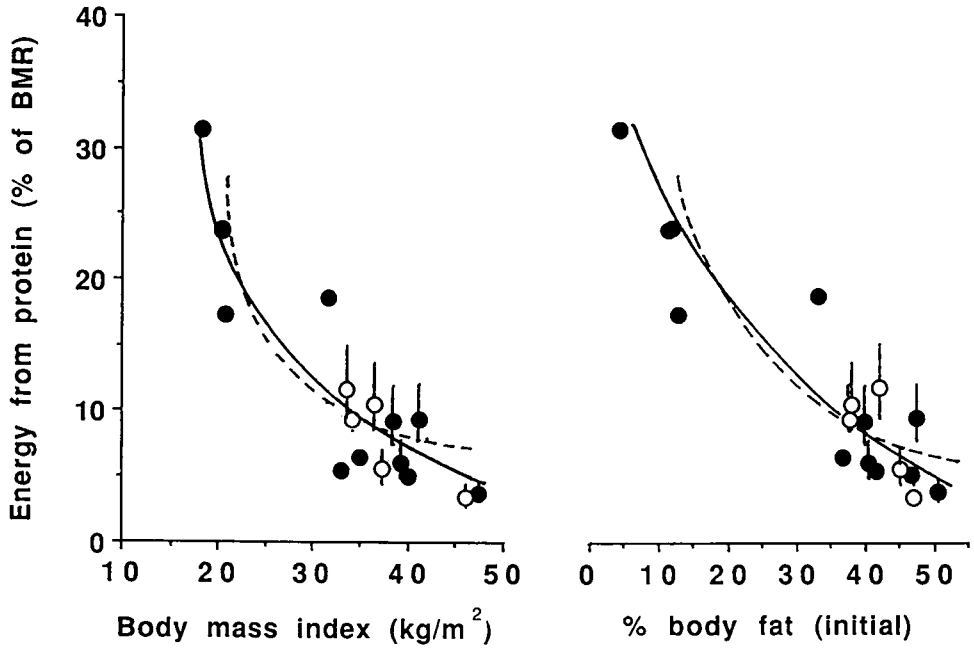

Figure 2: The effect of initial body mass index (left) and percent body fat (right) on the contribution of protein oxidation to basal metabolic rate in subjects undergoing starvation (>16 days). Solid circles represent individual data (9M, 4F) and open circles group mean data. The dotted curve is theoretical, based on calculations similar to those in Tables 3 and 4, assuming the ratio of total energy expenditure to BMR is 1.3. From Elia, 1992 (3).

oxidation accounting for most of the remaining (see Table 1, Figures 1 and 2). After the first few days of starvation the liver converts fat to ketone bodies, which are then oxidised by many other tissues, accounting for about half of the non-protein energy expenditure. For example, ketone bodies replace glucose as the dominant energy source for the brain. Their circulating concentration rises up to about 50 times to attain a higher circulating molar concentration than any other substrate. However, differences in ketone body metabolism between lean and obese subjects during total starvation exist and are suggested by the following observations:

1. The circulating ketone body concentration rises more rapidly in lean subjects than obese subjects (Figure 4). The rise is even greater in children, indicating an independent age-related effect of starvation. It has also been reported that ketone body concentration rises more rapidly in adult females than in males (21,22), although the females studied had a greater percent body fat than the males [calculations based on equations of Black et al. (23), and the median (21) and mean (22) body mass index of the subjects studied]. Furthermore, in prolonged starvation, the rise may be greater in older rather than younger adults (24). Because a greater proportion of the lean adults shown in Figure 4 were male and younger, the results suggest that differences in body composition (rather than age/gender) are responsible for the variable hyperketonaemic response.
2. During the first few days of starvation the circulating concentration ratio of 3-hydroxybutyrate (BOH) to acetoacetate (AcAc), which is an indicator of mitochondrial redox state, can be as much as 2-fold greater in lean than obese subjects (Figure 5).
3. At similar rates of net splanchnic ketone body production (or whole body tracer estimates of ketone body production), lean individuals have higher circulating ketone body concentrations (~80% greater) and a higher ratio of BOH:ACAC (25% to 30% greater) [data from various sources have been summarised by Elia (20)].
4. Differences in ketone body metabolism exist in individual tissues. For example, after 3 days of starvation, the uptake of ketone bodies (BOH and AcAc) by the forearm muscle of obese individuals can account for about 50% of the oxygen used (Figure. 6). Later on during starvation, non-esterfied fatty acids (NEFA) displace ketone bodies as the major energy source for muscle so that ketone bodies account for 18% of the O_2 use (25) [only 10% in some studies (27)]. Indeed, some of the carbon taken up as AcAc is released as BOH. This contributes to both the rise in circulating BOH (and total ketone body) concentration and the ratio of BOH:AcAc. The result is that ketone bodies can be channeled towards the brain, where they become the dominant energy

Table 1. Hypothetical values of body composition, fuel availability, and survival time in a lean 70 kg man and an obese man twice ideal body weight

	Lean subject	Obese subject
Initial		
Body weight (kg)	70	140
Fat (kg)	9.0	61.5
Protein (kg)	12.2	15.7
Glycogen (kg)	0.3	0.4
Loss during starvation		
Weight (% of initial)	38.0	69.0
Weight (kg)	26.6	96.6
Fat (kg)†	8.0	61.5
Protein (kg)‡	4.6	8.1
Glycogen (kg)	0.3	0.4
Available energy (kcal) during starvation		
Fat	75,200 (77.6%)	568,700 (93.8%)
Protein	20,400 (21.1%)	36,000 (5.9%)
Glycogen	1,260 (1.3%)	1,680 (0.3%)
Total	98,860 (100.0%)	606,380 (100.0%)
Mean daily total energy expenditure (kcal/day)§	1500	2260
Survival time (days)	65	270

*The composition of the body in the lean subject is based on reference man (8), and the excess weight in the obese individual is assumed to be 75% fat and 25% fat-free tissue.
†Fat accounts for 30% of the loss of body weight in the lean subject and 63% of the loss in the obese subject. Fat-free tissue accounts for 70% of the weight loss in the lean subject and 37% in the obese subject.
‡Assuming 1 gN = 6.25 g protein, there is a loss of 24.0 gN/kg loss of body weight in the lean subject and 12.4 gN/kg in the obese subject.
§These are only approximate values partly because of the variable decrease in resting energy expenditure below that predicted for normal individuals of the same weight (~25% during long-term starvation in lean individuals; Elia, 1992 (3)), and partly because of the variable decrease in physical activity.
Based on Elia, 1992 (3).

source during prolonged starvation. In lean individuals, the metabolism of ketone bodies in forearm muscle during early starvation differs from that in the obese in two ways. First, their contribution to energy metabolism is less than in the obese [O_2 equivalent in the lean: ~5% after an overnight fast; ~10% after 36 to 40 hours of starvation; and ~20% after 60 to 66 hours of starvation; Figure 6 (26)]. Second, by 60 to 66 hours of starvation, some of the AcAc taken up is already released as BOH, a phenomenon that was observed in obese individuals only during prolonged starvation.

The cause and significance of the apparent differences in ketone body and fatty acid forearm metabolism between lean and obese subjects during early starvation are unclear. However, the lean subjects investigated by Elia et al. (26) were all young healthy adults, whereas the obese subjects studied by Owen & Reichard (25) were older, mainly female subjects, some of whom suffered from other conditions (diabetes, heart failure, polycythaemia). Sex, age, and obesity can affect muscle size and metabolism (including insulin sensitivity), but the extent to which these factors are responsible for the differences in muscle metabolism is uncertain. Ketone bodies have been implicated in sparing protein, either directly or indirectly, e.g., by replacing glucose as a fuel for the brain. However, the greater rise in ketone body concentration in lean subjects during early starvation fails to reduce N excretion below that observed in the obese. It is clear that there is still some uncertainty about the factors that control protein breakdown during early starvation, which will often produce a transient increase in protein oxidation, about 2–3 days after the onset of starvation (3,6).

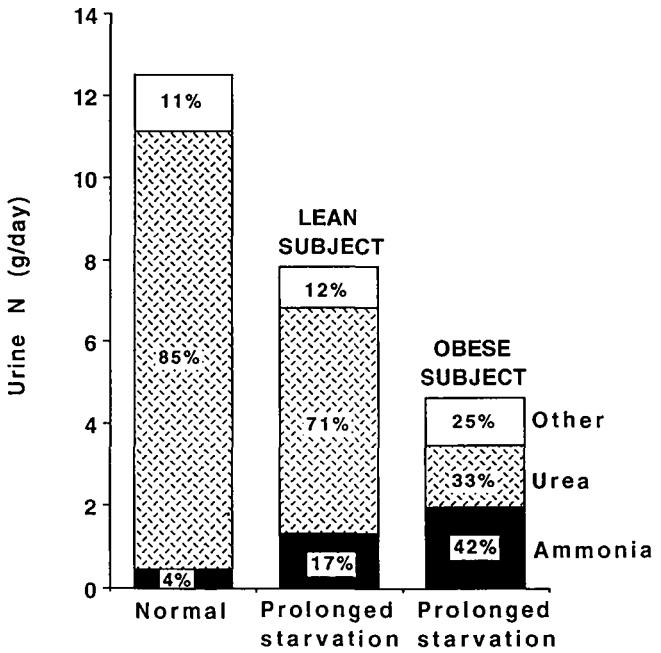

Figure 3: Distribution of urine N in the fed state (normal – intake of 90 g dietary protein/day) and after 30 to 40 days starvation in lean and obese subjects. Data based on Elia, 1998 (11); Owen et al., 1969 (10); Benedict, 1915 (5); Cahill, 1970 (12); and Elia et al., 1984 (13). The data for the starving lean subject are based on Benedict, 1915 (5) (day 30 of starvation). The rise in urine ammonia occurs within a few days of the start of starvation (5,10), and the absolute excretion rate at this time may be greater than in prolonged starvation. Based on Elia, 1999 (11).

Glucose Metabolism

After the first 2 to 3 days of starvation, virtually all the net glucose formed is derived from glycerol (a constituent of triacylglycerol) and protein. Using data from Table 1, it can be calculated that during prolonged starvation, protein can potentially provide more net glucose than glycerol in both lean and obese subjects. However, since the ratio of available protein to triacylglycerol (fat) is greater in the lean, the ratio of potential glucose derived from protein relative to that derived from glycerol is expected to be 4-fold greater in the lean (Table 3). Similar calculations can be made using measurements of urine N excretion and basal metabolic rate (BMR) [lean subjects, 7.8 gN/day and BMR 1130 kcal/day on day 31 of starvation (5), obese subjects, 5 gN/day and BMR 1450 kcal/day at 5 to 6 weeks of starvation (12)]. Calculations, using similar assumptions to those used to construct Table 3, show that the ratio of glucose derived from protein to that from glycerol (under basal metabolic rate conditions) is again greater in lean than in the obese. Indeed under these conditions, glycerol contributes 44% to the net glucose production in the obese (total 36.4 g/day with 16.1 g/day from glycerol), and 24% in the lean (total 41.8 g/day with 10.1 g/day from glycerol).

Another important aspect of carbohydrate metabolism is the site of net glucose production during starvation. The kidney is a potentially gluconeogenic tissue, but under normal circumstances it contributes little to whole body gluconeogenesis, which occurs almost entirely in the liver. During starvation, amino acids such as glutamine are metabolised in the kidney to yield ammonia, which is then excreted in urine in increased amounts (Figure 3). At the same time, the kidney converts the glutamine carbon skeleton to glucose. Early studies of prolonged starvation (35 to 41 days) suggested that the kidneys of obese individuals release almost as much glucose into the circulation (220 mmol/day) as the liver (250 mmol/day) (10). More recent studies [21 days of starvation (28)], however, suggest that they release more glucose into the circulation than the liver (324 vs. 366 mmol/day). Although comparable information is not available in lean subjects undergoing prolonged starvation, it is clear that the lean metabolize more amino acids (greater urine N excretion) than obese subjects, but they do not excrete more urinary ammonia (Figure 3). This suggests that during prolonged starvation lean subjects produce much more glucose in the liver than in the kidney (cf obese).

Apart from differences in the rates and sites of glucose formation, changes in glucose tolerance during starvation

Table 2. Comparison of the changes in leucine concentration and ^{14}C-leucine kinetics in lean and obese subjects between an overnight fast (12 hours) and 60 hours of starvation

	Lean		Obese	
	12 hours	**60 hours**	**12 hours**	**60 hours**
Leucine (μmol/L)	93±8	252±8*	113±9	199±8*
Leucine oxidation (μmol/min/kg)	0.18±0.03	0.42±0.06*	0.23±0.04	0.27±0.05
Leucine rate of appearance (μmol/min/kg)	1.51±0.2	2.3±0.42*	1.34±0.2	1.12±0.15

*Significant differences compared to values obtained after an overnight fast.
Based on Umpleby et al. 1995 (19).

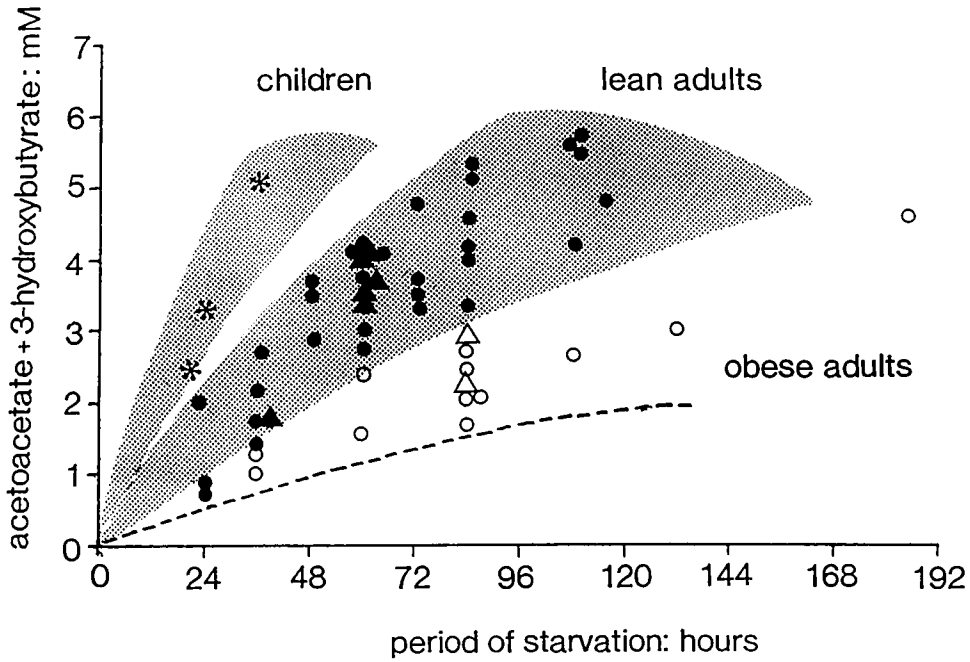

Figure 4: The effect of total starvation on the circulating concentration of ketone bodies [3-hydroxybutyrate (BOH) plus acetoacetate (AcAc)] in lean (solid symbols) and obese adults (open symbols) and children 5 to 7 years. Each point represents results of groups of individuals. From Elia, 1991 (20).

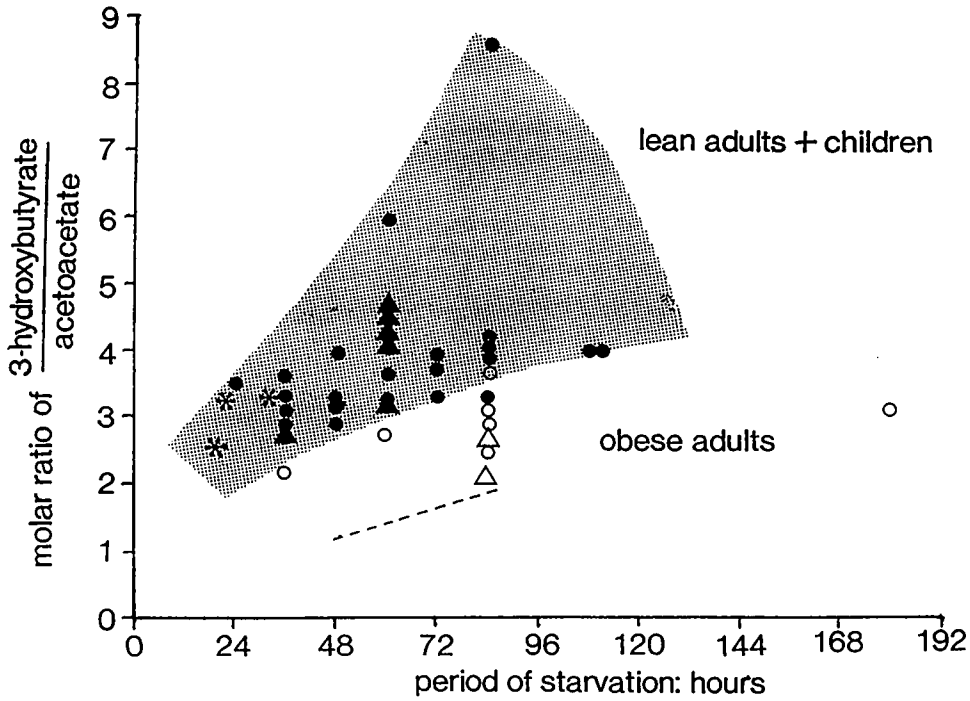

Figure 5: Effect of total starvation on the circulating molar ratio of 3-hydroxybutyrate (BOH) to acetoacetate (AcAc) in lean (solid symbols) and obese subjects (open symbols). From Elia, 1991 (20).

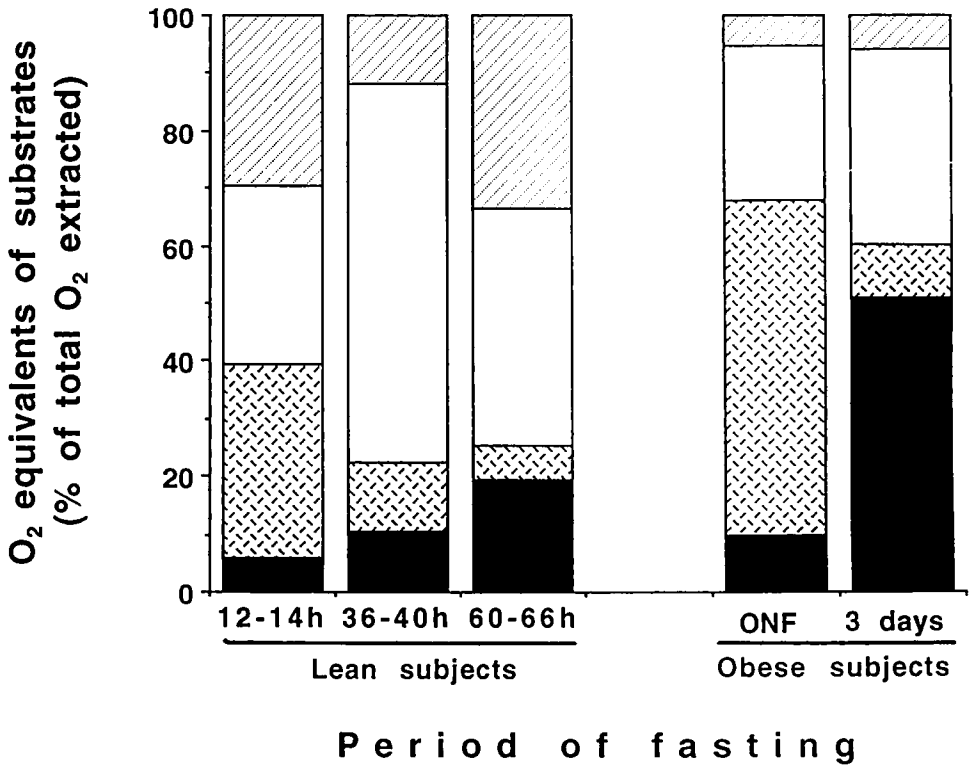

Figure 6: O_2 equivalent of NEFA, glucose, and ketone bodies as percentage of total O_2 extracted by forearm muscle of lean and obese subjects at various stages of starvation. Solid square = Ketone bodies (AcAc+BOH); open square = glucose; dotted square = NEFA; hatched square = other substrates; ONF = overnight fast. From Owen & Reichard, 1971 (25) and Elia et al (26).

also appear to differ between lean and obese subjects. For example, after 6 days starvation, glucose tolerance has been reported to deteriorate more in lean subjects than obese subjects (increase in glucose concentration of 526±27 mg/100 mL in the lean vs. 266±40 mg/100 mL in the obese between the first and second glucose tolerance test; $p<0.001$) (29). Several factors may be responsible for this difference, including incremental changes in circulating ketone body concentrations (4.85 vs. 6.39 mmol/L) and NEFA (409 vs. 736 μmol/L), which were found to be significantly greater in the lean (NEFA and ketone bodies compete with glucose for uptake and metabolism in muscle).

Table 3. Estimation of potential glucose formation from glycerol and protein during the entire period of starvation in lean and obese subjects

	Lean	Obese
Available protein (g)	17,760*	33,300*
Available fat (g)	75,200*	568,700*
Glucose from protein (g)†	11,544	21,645
Glucose from glycerol (g)‡	833	6,299
Glucose from protein/ glucose from glycerol	13.86	3.44

*Values from Table 1.
†Assumes that 65% of amino acids are converted to glucose.
‡Assumes that 2 moles of glycerol, present in 2 mole triglyceride (34,000 kJ/mole; 8126 kcal/mol), are converted to 1 mole of glucose.

In summary, the standard textbook descriptions of metabolism during prolonged human starvation, which are largely based on studies in the obese, represents only one end of the metabolic spectrum. These responses should be clearly differentiated from those of lean subjects, especially since many of them have important adaptive implications for survival. The underlying mechanisms require investigation.

References

1. **Wu G, Marliss EB.** Interorgan metabolic coordination during fasting and underfeeding: an adaptation for mobilizing fat while sparing protein in humans. In: Anderson GH, Kennedy SH, eds. *The Biology of Feast and Famine: Relevance to Eating Disorders.* New York : Academic Press; 1992;219–24.
2. **Voit E.** Die grösse desulfovibrio giwizsszerfalles im hunger. *Z F Biol.* 1901;16:167–95.
3. **Elia M.** Effect of starvation and very low calorie diets on

protein-energy interrelationships in lean and obese subjects. In: Scrimshaw NS, Schürch B. *Protein–Energy Interactions.* Lausanne, Switzerland: Nestlé Foundation; 1992.
4. **Henry CJK, Rivers JPW, Payne PR.** Protein and energy metabolism in starvation reconsidered. *Eur J Clin Nutr.* 1988; 42:543–8.
5. **Benedict FG.** *A Study of Prolonged Fasting.* Carnegie Institute of Washington, Publication No. 203, Washington DC; 1915.
6. **Goschke H, Stahl M, Tholen H.** Nitrogen loss in normal and obese subjects during total fast. *Klinische Wochenschrift.* 1975;53:605–10.
7. **Takahira H.** Metabolism during fasting and subsequent refeeding. *Imperial Govt. Institute for Nutrition, Tokyo.* 1925; 1:63–82.
8. **Snyder WS, Cooke MJ, Nasset ES, Karhausen LR, Howells GP, Tipton IH.** *Report of the Task Group on Reference Man. International Commission on Radiological Protection No. 23.* Oxford: Pergamon Press; 1975.
9. **Cherel Y, Robin J–P, Heitz A, Calgari C, Le Maho YL.** Relationships between lipid availability and protein utilisation during prolonged fasting. *J Comp Physiol B.* 1992;162: 305–13.
10. **Owen OE, Felig P, Morgan AP, Wahren J, Cahill GF J.** Liver and kidney metabolism during prolonged starvation. *J Clin Invest.* 1969;48:574–83.
11. **Elia M.** Metabolic response to starvation, injury and sepsis. In: Payne–James J, Grimble G, Silk D. *Artificial Nutritional Support in Clinical Practice.* London: Edward Arnold; 1999; (in press).
12. **Cahill GF.** Starvation in man. *N Engl J Med.* 1970;282: 668–75.
13. **Elia M, Crozier C, Neale G.** Mineral metabolism during short-term starvation in man. *Clin Chim Acta.* 1984;139: 37–45.
14. **Walser M, Bodenlos LJ.** Urea metabolism in man. *J Clin Invest.* 1959;38:1617–26.
15. **Danielson M, Jackson AA.** Limits of adaptation to a diet low in protein in normal man: urea kinetics. *Clin Sci.* 1992;83: 103–8.
16. **Child SC, Soares MJ, Reid M, Persaud C, Forrester T, Jackson AA.** Urea kinetics varies as Jamaican women and men in relation to adiposity, lean body mass and protein intake. *Eur J Clin Nutr.* 1997;51:107–15.
17. **Moran BJ, Karran SJ, Jackson AA.** Enhanced retention of urea nitrogen in patients on total parenteral nutrition for intestinal failure. *Clin Nutr.* 1991;10:67–70.
18. **Wheeler RA, Griffiths DM, Jackson AA.** Urea kinetics in neonates receiving total parenteral nutrition. *Arch Dis Child.* 1993;69:24–7.
19. **Umpleby AM, Scobie IN, Boroujerdi MA, Sönksen PH.** The effect of starvation on leucine, alanine and glucose metabolism in obese subjects. *Eur J Clin Invest.* 1995;25:619–26.
20. **Elia M.** The inter-organ flux of substrates in fed and fasted man, as indicated by arterio–venous balance studies. *Nutr Res Rev.* 1991;4:3–31.
21. **Goschke H, Girard J, Stahl M.** Der stoffwechsell bei vollstandigem fasten. Unterschiedliches verhalten bei mannern und frauen sowie bei normalpersonen und adiposen. (Metabolic differences between males and females and between normal and obese subjects during a total fast.) *Klinische Wochenschrift* 1976;54:527–53.
22. **Haymond MW, Karl IE, Clarke WL, Pagliara AS, Santiago JV.** Differences in circulating gluconeogenic substrates during short term fasting in men, women and children. *Metabolism* 1982;31:33–42.
23. **Black D, James WPT, Besser GM, et al.** 1983 Obesity. A report of the Royal College of Physicians. *J Royal Coll Phys (London).* 1983;12:5–65.
24. **Hall SEH, Wastney ME, Bolton TM, Braaten JT, Berman M.** Ketone body kinetics in humans: the effects of insulin dependent diabetes, obesity and starvation. *J Lipid Res.* 1984; 25:1184–94.
25. **Owen OE, Reichard GA.** Human forearm metabolism during progressive starvation. *J Clin Invest.* 1971;50:1536–45.
26. **Elia M, Wood S, Khan K, Pullicino E.** Ketone body metabolism in lean male adults during short-term starvation, with particular reference to forearm muscle metabolism. *Clin Sci.* 1990;78:579–84.
27. **Hagenfeldt L, Wahren J.** Human foreman muscle metabolism during exercise VI. Substrate utilization in prolonged fasting. *Scand J Clin Lab Invest.* 1971;27:299–306.
28. **Owen OE, Smalley KJ, D'Alessio AD, Mozzoli MA, Dawson EK.** Protein, fat, and carbohydrate requirements during starvation: anaplerosis and cataplerosis. *Am J Clin Nutr.* 1998; 68:12–34.
29. **Goschke H.** Mechanism of glucose intolerance during fasting: differences between lean and obese subjects. *Metabolism.* 1977;26:1147–53.