Insulin Resistance in Catabolic Diseases

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With remarkable intuition, John Hunter [1] in 1794 described the response to injury as follows: ‘Impressions are capable of producing or increasing natural actions and are then called stimuli: they are likewise capable of producing too much action as well as depraved, unnatural or what we commonly called diseased actions’. Scientific studies over the last century have lent support to this hypothesis in which the neuroendocrine, cytokine and consequent metabolic responses to injury are essential to survival, but when carried to extreme may put survival in jeopardy.

Metabolic Response to Injury

In the 1920s, Cuthbertson [2] described the increased metabolic rate and nitrogen loss caused by injury. These changes are accompanied by increased lipolysis to provide energy from fat, and by initial glycogenolysis followed by accelerated gluconeogenesis from protein [3, 4] in order to provide not only essential glucose for the brain but also meet the needs of the injured tissue [5], which respires glucose anaerobically. Metabolites are therefore diverted from nonessential tasks such as physical activity to the needs of healing tissue and the immune system. If sufficiently severe and prolonged, however, the response can lead to severe wasting and impaired function and survival. The phases of the response to injury have been divided into a brief initial shock or ebb phase when metabolism may be depressed, then the flow or catabolic phase, followed by the convalescent, recovery or anabolic phase in which lost tissue is reformed. During the flow phase, salt and water are retained and the extracellular fluid space is expanded [6, 7]. Convalescence is heralded by a return of the ability to excrete an excess salt and water load. Moore [7] coined the terms ‘sodium retention’ and ‘sodium diuresis’ to describe this phenomenon.
These metabolic changes are mediated by cytokine and neuroendocrine responses.

**Endocrine Response to Injury**

Between 1943 and the mid-1980s, the increased secretion of the catabolic hormones, cortisol [8, 9], catecholamines [10] and glucagon [11], were reported. Studies [12] infusing a combination of these stress hormones in healthy humans were able to mimic some of the metabolic changes observed after injury, although these were smaller than those seen in patients.

**Insulin Secretion and Resistance**

In 1853, Reynoso [13] reported glycosuria associated with ether anesthesia, and in 1877 Bernard [14] described the hyperglycemia which accompanied hemorrhagic shock. A series of studies during the 20th century showed hyperglycemia and glucose intolerance associated with surgery, anesthesia, injury and burns (described as the pseudo-diabetes of burns). As the immunoassay for insulin became available in the 1960s, it became possible to study changes in insulin secretion. In 1966, Ross et al. [15] demonstrated insulin resistance after surgery, and this was subsequently confirmed by Giddings et al. [16]. Between 1967 and 1971, we [17–19] reported hyperglycemia, glucose intolerance and high free fatty acid levels in the shock phase of injury, associated with suppressed insulin secretion, due probably to α-adrenergic stimulation. A week after injury, there was persistent hyperglycemia and glucose intolerance, with failure of the normal suppression of plasma fatty acids after glucose infusion. These later changes were associated with higher than normal insulin levels. We therefore proposed that, after the acute phase of injury, insulin suppression gave way to insulin resistance in terms of both carbohydrate and fat metabolism, and suggested that these changes in insulin secretion, combined with the increase in catabolic hormones described by others, might be responsible for some of the changes in protein metabolism after injury [20] (fig. 1). These observations were confirmed by a series of elegant studies by Wilmore et al. [21] using glucose clamp and tracer techniques to show that, in the flow phase of injury, the maximal rate of total glucose disposal is reduced, suggesting a post-receptor insulin resistance in peripheral tissue. Other studies, such as those by Carlson and Little [22], have shown that, despite an overall increased turnover of glucose, there are differential changes in glucose metabolism between tissues, with diminished storage as glycogen, diminished oxidation in some tissues and increased oxidation in others, particularly at the site of injury. Biolo et al. [23] and Sakurai et al. [24] have also shown that, for many weeks after burn injury,
there is diminished protein synthesis in muscle cells secondary to impaired amino acid uptake. This phenomenon could be reversed using high doses of insulin with amino acids, but not by increasing the amino acid supply alone.

Recent studies by Thorell et al. [25] and Soop et al. [26] using pre- and post-operative glucose clamps have confirmed insulin resistance after surgery and shown that by giving a glucose drink 12 and 2 h preoperatively, thereby putting the patient into a metabolically ‘fed’ state, not only is postoperative insulin resistance reduced, but protein losses are lessened, showing again that there are close links between insulin resistance and protein metabolism. Interestingly, their simple preoperative glucose treatment resulted in improved clinical outcome and shorter hospital stay.

**Insulin Therapy**

*Effects on Protein Metabolism*

Sakurai et al. [24] have summarized the goal of nutritional therapy in critical illness as follows: ‘The goal of the nutritional management of critically ill patients is to promote wound healing and resistance to infection, while preventing persistent loss of muscle protein, since survival of critically ill patients is inversely correlated with loss of lean tissue’. In a recent review, however, Campbell [27] wrote: ‘In the severely septic and injured patient, an improvement of nutritional status or increase of lean body mass by nutritional support alone is likely to be impossible. The most one can hope for is to slow the rate of decline. If lean body mass is to be maintained, it is likely that pharmacological methods will have to be found for doing so.’
Following our initial observation of changes in insulin secretion after injury, we tested our hypothesis that insulin therapy might be used to reduce protein catabolism, on the basis that if catabolism of endogenous substrates could be blocked, it would allow the better utilization of exogenous substrates administered during oral feeding or artificial nutritional support. In other words, it was an attempt not just to block catabolism, but to divert substrates into anabolic pathways. In vitro studies by Manchester in the late 1960s also demonstrated the effect of insulin on amino acid transport into cells and protein synthesis [28, 29]. Initial studies on burned patients [30] confirmed this hypothesis, showing large reductions in urea and potassium output when insulin was administered in large doses of up to 600 units/day, accompanied by glucose infusion of 250–500 g/day and oral food intake. Since these observations were not made by comparison with a control group of isocalorically fed patients, we undertook further studies [31] comparing 3 groups receiving the same nitrogen dose of 9.4 g/day, but three different isocaloric energy sources, (1) sorbitol and intralipid, (2) glucose alone, and (3) glucose plus insulin, to give a nonprotein energy intake of 2,400 kcal. The blood glucose and plasma insulin levels achieved are shown in table 1. The study was also repeated using the same nonprotein energy intake but giving 18.8 g nitrogen [32]. The insulin regime caused a significant reduction in protein catabolism compared to the other two regimes, but only in the catabolic patients, being proportional to the degree of injury and degree of pretreatment protein catabolism (fig. 2). Figure 3 shows a comparison of the 2 studies relating the urea production rate (UPR) on glucose alone to the percent change in UPR when high dose insulin was given. It can be seen that the anticitabolic effect of insulin was only seen when the initial UPR exceeded 15 g/24 h. It can also be seen that, although the higher nitrogen dose appeared to be utilized in the most catabolic patients, the excess over requirements was simply converted to urea in the noncatabolic group. Similar observations were made in burned patients by Long et al. [33], who found that negative nitrogen balance decreased as the glucose dose was increased, but only until this reached the metabolic rate of the patient. Any further reduction in protein catabolism could only be achieved if insulin was added. This group also showed improved

### Table 1. Blood glucose and serum insulin levels with different substrates, showing pharmacological levels of insulin in the glucose/insulin group

<table>
<thead>
<tr>
<th>Energy substrate</th>
<th>Blood glucose (mmol)</th>
<th>Serum insulin, mU/l</th>
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</thead>
<tbody>
<tr>
<td>Sorbitol/intralipid</td>
<td>6.5 ± 2.6</td>
<td>29.4 ± 34</td>
</tr>
<tr>
<td>Glucose</td>
<td>11.0 ± 3.3</td>
<td>81.0 ± 47</td>
</tr>
<tr>
<td>Glucose/insulin</td>
<td>7.5+</td>
<td>222.6 ± 219</td>
</tr>
</tbody>
</table>

See text and Woolfson et al. [31] and Woolfson [32].
**Fig. 2.** Nitrogen balance (g/24 h) in burns. Differential effects of added insulin according to the initial metabolic state of the patients. UPR = Urea production rate (mmol/24 h; mean ± standard deviation). Adapted from Woolfson [32].

**Fig. 3.** Comparison between infusion of glucose alone and glucose + insulin on the urea production rate at two levels of nitrogen administration. UPR = Urea production rate (mmol/24 h); N = nitrogen. Adapted from Woolfson [32].
nitrogen balance across the limbs using insulin with branched chain amino acids [34].

During the 1980s, the use of glucose and insulin came under a cloud following studies showing that glucose administration rates above 300 mg/kg/h had several adverse effects, particularly in critically ill patients. CO2 production and oxygen consumption increased, thereby causing respiratory problems [35]. Fatty liver and cholestasis were induced. Fat stores increased but not lean mass. Hyperglycemia was also caused and linked to increased risks of secondary infections [36]. It was assumed, wrongly as it turns out, that using insulin would exacerbate some of these problems and the doses of carbohydrate in nutritional formulae was reduced to a level which reduced the risk of hyperglycemia. Attention therefore switched to the use of growth hormone which was also shown to have protein-sparing effects in critical illness. Unfortunately, however, two major trials [37, 38] showed that the use of growth hormone was associated with increased mortality under these circumstances.

During the last 10 years insulin has had a renaissance [39]. In an elegant series of studies, Biolo et al. [23] and Sakurai et al. [24] have shown that, in healthy subjects, exogenous insulin stimulates protein synthesis but has no effect on protein breakdown. The amino acid supply was found to be rate-limiting for this anabolic effect. These studies confirmed in vivo the work of Manchester [28, 29] in vitro 30 years previously. In burned patients, studied several weeks after injury, exogenous insulin given with amino acids, eliminated the negative nitrogen balance across muscle, increasing protein synthesis by 350% due to a sixfold increase in amino acid transport into muscle cells.

From all these studies, it is possible to conclude that not only does insulin have its well-known anabolic effects in relation to carbohydrate and fat metabolism, but that in catabolic illness it effectively reduces protein catabolism and helps to preserve lean mass. None of these studies, however, measured clinical outcome.

**Effects on Fluid and Electrolyte Balance**

Our early studies showed, not surprisingly, reduced potassium excretion pari passu with reduced nitrogen excretion, since potassium is linked both to glycogen and protein intracellularly and is lost to the cell and excreted as the substrates are catabolized. Conversely, with the onset of anabolism in convalescence, and the resynthesis of glycogen and protein, potassium is taken up by the cell with abrupt falls in serum potassium concentration unless additional potassium is supplied. This forms part of the so-called refeeding syndrome. It may also be accompanied by significant reductions in phosphate levels. It is important, therefore, to monitor these in any patient receiving nutritional support or glucose and insulin infusions.
Many of the burned patients, however, were in large positive salt and water balance days or weeks after the initial injury, due to the administration of fluids during resuscitation and subsequently. This positive balance was accompanied by edema and often by hyponatremia. To our surprise, insulin, but not glucose alone, caused a dramatic increase in salt and water excretion (fig. 4), and a rise in plasma sodium concentration [40]. We speculated that this might be due to the cell membrane effects of insulin, reversing the ‘sick cell syndrome’ described by Flear and Singh [41] in critically ill patients and confirmed by Campbell et al. [42] in muscle biopsies from critically ill patients which had higher sodium and lower potassium content than control biopsies from normal subjects. This hypothesis would accord with observations by Zierler [43] of the effect of insulin on cell membranes.

We extended these observations to other conditions associated with salt and water retention, such as heart failure, and found a similar effect. These results contrast with the effect of insulin in normal insulin-resistant, diabetic and obese individuals, in whom insulin causes renal sodium retention.

**Fig. 4.** Comparison of the effect of glucose and insulin (a) versus the effect of insulin alone (b) on the urinary excretion of water, sodium and potassium, and the corresponding changes in serum sodium and potassium in severely burned patients with ‘sick cell’ syndrome.
Indeed the introduction of insulin in a type-1 diabetic can sometimes cause edema.

**Insulin in Cardiovascular Disease**

We used the same regimen of 50% glucose, potassium to maintain normokalemia, and high-dose insulin in patients with severe congestive cardiac failure and found that, within minutes of starting the infusion, a large salt and water diuresis began associated with a rise in blood pressure and, in 1 case, reversion from atrial fibrillation to sinus rhythm [44]. These changes suggested a similar membrane effect to that we postulated in burned patients. In a recent study on the effect of insulin in patients with heart failure, Parsonage et al. [45] found it to cause a fall in heart rate, a rise in cardiac output and increased muscle but decreased splanchnic blood flow. These authors also pointed out that insulin resistance is a feature of heart failure. The positive outcome results of the DIGAMI study [46] using insulin to maintain normoglycemia in diabetics with myocardial infarction recall the original description by Sodi-Pallares et al. [47] of the use of insulin, glucose and potassium after myocardial infarction. Similar positive effects of insulin were observed by Svedjeholm et al. [48] in patients with severe cardiac failure following cardiac surgery.

**Insulin, Blood Glucose and Clinical Outcome**

The hyperglycemic and glucose-intolerant responses to illness have been known for 150 years, but their potential for harm, with increased susceptibility to infection and impaired immune response, was only understood relatively recently. In a study of burned children Gore et al. [49] found a lower mortality, incidence of bacteremia and fungemia, and the number of skin-grafting procedures were lower when normoglycemia was maintained with insulin.

In a landmark study on 1,548 adult patients in intensive care, Van den Berghe et al. [50] used intensive insulin therapy to maintain blood glucose at 110 mg/dl or less compared with a control group whose blood glucose ranged from 180 to 200 mg/dl. Intensive insulin treatment reduces episodes of septicemia by 46%, renal failure requiring hemodialysis by 41%, and critical illness polyneuropathy by 44%. Intensive care unit mortality was reduced by 45%, attributable to the prevention of multiple organ failure in longer stay patients. An interesting question is whether these striking beneficial clinical effects are due to blood glucose control or to the other effects of insulin or to both. Van den Berghe et al. [50, 51] have argued persuasively that the maintenance of strict normoglycemia was the main effect, with a direct stepwise relationship between blood glucose and the complication and mortality rate.
A similar relationship was shown between the complication rate and triglyceride levels which were also reduced to normal by insulin treatment. The daily dose of insulin given was also modest, 70 U/day, lower than our own and other studies showing beneficial metabolic effects. Whatever other effects insulin treatment might have had, however, there seems little doubt that tight and accurate blood glucose control is now an established and vital part of management in critical illness.

**Insulin Dosage**

The doses of insulin used in most of the studies described are of a pharmacological order exceeding those used in maintenance therapy of type-1 diabetics or even in the treatment of ketoacidosis. Woolfson [52] has described a useful algorithm for insulin treatment in critical care (table 2), which takes into account not only the prevailing blood glucose but also its direction of change from the previous measurement.

**Conclusions**

The response to illness, injury and surgery is characterized not only by the classical metabolic changes of increased metabolic rate and negative nitrogen balance, but by hyperglycemia and glucose intolerance caused by α-adrenergic suppression of insulin release in the acute shock phase or during surgery,
and by insulin resistance in the flow or postoperative phase. These changes are correlated with the degree of negative nitrogen balance which may be reduced by preoperative carbohydrate loading in elective surgery or by insulin, glucose and potassium given as adjunctive treatment with nutritional support in catabolic illness or after major trauma. Insulin treatment under these circumstances not only reduces protein catabolism, but also maintains normoglycemia, reduces lipolysis, improves cardiac function in heart failure, enhances salt and water excretion, and has now been shown to improve clinical outcome from critical illness. Insulin treatment to maintain strict blood glucose control is now established as a crucial part of critical care management.

References

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Discussion

Dr. Shenkin: Can I take up the point which Dr. Allison raised about the history of this extraordinary series of findings. I am old enough to remember the excitement when Hinton et al. published these remarkable physiological changes, and then things went quiet for nearly 30 years. I was just wondering if Dr. Allison could expand on why this happened. What were the complications of the high-glucose therapy? Was it because total parenteral nutrition was not used appropriately? What complications occurred and why did it take so long to have this further set of studies?

Dr. Allison: Glucose in high doses fell into disrepute. We didn't actually give very high doses of glucose, but those who were giving high doses of glucose brought it into disrepute because of its effect on increased demand for gas exchange and fatty liver, and all the other complications of a high-glucose intake. It was thought mistakenly that giving insulin would make it much worse, and some people reduced the level of glucose intake to try and control the glycemia. Along came growth hormone and we were diverted into the red herring of growth hormone because lots of studies showed positive nitrogen balance and everybody thought this was marvelous until they actually tested the clinical outcome. I think the main reason is that Dr. Van den Berghe and her colleagues were not around, and we were unable to do the proper study, as they have done, on clinical outcome. So in other words if we had done a proper study on clinical outcome, we might have avoided going into the wilderness for 20 years.

Dr. Bunnag: Van den Berghe et al. [1] showed that seemingly intensive insulin therapy can have very small adverse effects like hypoglycemia if you monitor very closely. Could you comment on that?

Dr. Mesotten: There were almost no complications. The most important part is just the education and training of the nursing staff that glucose should be monitored every half an hour in the first phase. What was really clear from the studies is that, in the first day or the first few days, when you are trying to titrate the insulin you really need close monitoring. As soon as the patient is stable after a few days, once every 2 h, even every 6 h is more than enough. The events of hypoglycemia usually happen due to mistakes, for example when a patient went to radiology and parenteral nutrition was disconnected while the insulin was still running. Then you get hypoglycemia, otherwise it seems to be fairly stable.

Dr. Sudomo: There are now immunonutrition products on the market that contain glutamine and arginine. What do you think about this?

Dr. Allison: Immunonutrition I think is a subject for another day.

Dr. Sudomo: My other question is about hypoglycemia. Your method for giving high-dose insulin is very dangerous.

Dr. Allison: What is dangerous?

Dr. Sudomo: Intensive insulin therapy. It is not possible for all hospitals to do close monitoring.

Dr. Allison: A car is very dangerous until you learn how to use it.
**Dr. Sudomo:** I mean the complication of hypoglycemia.

**Dr. Allison:** It is not dangerous.

**Dr. Basu:** The Van den Berghe study really is a landmark study, there is no question about that. I have three specific questions though. Were the insulin concentrations measured in a conventional versus an intensive treatment and, if so, what were the levels? Because the question comes to the chicken or the egg, is it the glucose lowering or is it the insulin hormone as such that is contributing to reduced mortality? Did you actually measure hepatic glucose production in sick patients using tracers and things like that? Was the change in growth hormone concentration due to the lowering of glucose levels or was it actually an insulin effect?

**Dr. Mesotten:** I will answer step by step. Your first question about whether it is insulin or glucose: we did not measure insulin levels because there was such a difference in the insulin administered so that is probably an important effect. However, looking for example at the effects of therapy on the critical illness on polyneuropathy, I think we cannot delineate from this study whether it is insulin or glucose, and it is the same for all the others. We can only speculate on that. As to your second question: yes, we looked at gene expression levels and at protein, for example BP1, in the serum for several reasons. First of all we had an indication of where glucose was going and, I agree, these are only a few steps in the complex intermediate metabolism so we have to look at genes or proteins. However we are embarking on some alternative studies to look at whether it is true or not that it is an uptake in skeletal muscle and not the suppression of the gluconeogenesis in the liver. What was the third question?

**Dr. Basu:** Whether the growth hormone response that you saw was because of the falling glucose level rather than a rise in insulin, because we do the insulin tolerance test to test growth hormone reserve.

**Dr. Mesotten:** You can't really tell from the study because you give insulin and you lower blood glucose. We were just really surprised but we were actually expecting a suppression of growth hormone and it went up. So we have no idea how to explain that actually.

**Dr. James:** Why do these patients then live when you give glucose and insulin? What actually are you doing? You produce changes in substrates that you measure in blood, but why do they live rather than die?

**Dr. Mesotten:** First of all, and I think this is really important, we have to clearly distinguish what we are talking about. The Van den Berghe study was specifically targeting normo-glycemia as in the treatment of diabetics, so we know that it has some beneficial effects. On the other hand, you also have the glucose insulin potassium infusions where normo-glycemia is not the target. I think those studies mainly target a change in the processing of glucose versus free fatty acids in muscle, for example. The only thing we can say is that there is a clear effect of intensive insulin therapy targeted at normo-glycemia. I think that should be distinguished, or the nutritional input should be checked as to whether or not is it with intermediate- or high-caloric intake. Here the patients were given about 25 kcal/kg/day.

**Dr. Allison:** I am just going to anticipate what you might say because the same effect was shown in diabetics having myocardial infarction, i.e. improved outcome with tight blood sugar control. It seems to have some effect. We know a lot of its other effects, e.g. on infection susceptibility and white cell function, and all the other things that it does.

**Dr. Kopelman:** I was going to bring that point up, but also the intriguing point you made about triglyceride levels being the marker of mortality, and the relationship between insulin and high- and low-density lipoprotein cholesterol which would suggest that insulin is a trigger for beneficial effects, not simply in relation to glucose but also to free fatty acid. This may well mean that it also enhances the action of intrinsic
growth hormone without having the detrimental effects of growth hormones that you see when you give them as an exogenous addition.

Dr. Bunnag: Do you have any data to show that the index of insulin sensitivity also predicts survival in these patients?

Dr. Mesotten: No, we don’t. We just have the insulin given versus the glycemia. We haven’t really measured insulin sensitivity.

Dr. Sitges-Serra: I haven’t had the opportunity to go through the manuscript so my interpretation can be completely biased. Is it possible that the problem is not in the insulin group but in the control group? It may be possible that because of overfeeding or glucose intolerance or severe disease, the problem is on the other side because this magic bullet in intensive therapy is puzzling. Giving a few grams of glutamine, for example, or branch chain amino acids or whatever you give, you find a difference in mortality. For a clinician that is rather puzzling. So in that kind of study there usually may be some problems in the control group, and whether you palliate that by giving insulin. Perhaps your tactics of feeding these patients are not appropriate and then you palliate that by giving insulin.

Dr. Allison: Are you talking about the Van den Berghe study, because it was a beautifully controlled study and design. I looked at the data and I think it would be very difficult to arrive at your interpretation.

Dr. Mesotten: I believe that insulin is important in redistributing all the substrates and enhancing metabolism in the cell. We did measure gene expression of insulin-regulated lipoprotein lipase (LPL) in skeletal muscle; however, we did not have enough samples to look at LPL in adipose tissue. There was no effect of intensive insulin therapy on LPL. We also measured free fatty acids and there was no effect. But all of us know that measuring free fatty acid levels can be tricky, and actually we were asked to leave it out. So the effects of intensive insulin therapy on lipid metabolism is still not clear. Where it works and how it works we have no idea, but we believe that insulin enhances metabolism in skeletal muscle at least.

Dr. Allison: Sometimes in human subjects it is not possible to dissect out the precise mechanisms and you have to go to an animal model. I know that Van den Berghe is studying animal models in this situation to try to work out some of these mechanisms. Have you any information on the results from that study? I think it was a mouse model, wasn’t it?

Dr. Mesotten: The model that we were using was a rabbit model with burns in the abdominal region. The rabbits are given parenteral nutrition and we follow blood pressure, etc. For example one of the mechanisms we were looking at was the function of insulin on the immune response and we saw that intensive insulin therapy increased the phagocytic function of macrophages, etc., so there was some explanation for the inflammatory effects. We did not really look at the mechanisms by which insulin affected the lipids.

Dr. Tantibhaedhyangkul: Did you measure oxygen consumption in the respiratory quotient?

Dr. Mesotten: No, we haven’t measured oxygen consumption.

Dr. Tantibhaedhyangkul: If you measure oxygen consumption in the respiratory quotient, it may give you an answer about the increase and distribution of substrates with a glucose effect.

Dr. Mesotten: We only had serum and postmortem liver and skeletal muscle samples to do the analysis and to give us a rough indication how things were working.

Dr. Allison: But just switching substrates is not going to explain the difference in mortality. It has got to be something pretty fundamental, like resistance to infection, effects on the immune system, perhaps effects on cardiorespiratory function and all these things.
Dr. Biolo: When I saw the title of your PhD thesis, I was hoping for a unifying hypothesis on the two major studies that came out in intensive care unit patients, growth hormone doubled mortality. You have just shown the effect of insulin on growth hormone concentration which is something that we know very well, but probably you have something more than this. We know that growth hormone has an important impact on insulin resistance. Do you have any other hypothesis on that, a unifying hypothesis?

Dr. Mesotten: Actually I am afraid I will have to disappoint you. I know the first part of my PhD is about the effects of growth hormone on critical illness, but as we can’t do any more growth hormone studies in patients, we did not have a human model, so I worked on rats. Our idea then was that growth hormone would induce insulin resistance, which I have shown. Then we thought that this insulin resistance had an effect on antitoxin processing through impairing normal bile salt, so I looked into different bile salt transporters and looked at those effects. However, I did not elaborate on the bile acid transporters in the insulin study because I did not have the time, so there is no unifying hypothesis. However if you give insulin to burn patients, IGF BP3 and IGF1 are lower. If you look at Takala’s growth hormone study, IGF1 is higher in the patients receiving growth hormone although they died. So IGF1 is a parameter of anabolism and good outcome.

Reference
