ESICM Satellite Symposium 2017

Chairperson of the Satellite Symposium: *Greet Van den Berghe, MD, PhD*

Nutritional Challenges in ICU patients

This symposium explored controversial aspects of the nutritional management of patients in the ICU. There are new concepts and old controversies such as the role of permissive underfeeding and the optimal timing of nutrient delivery. Glucose control is also one of such area where there is still no widespread agreement on optimal targets for blood glucose control in ICU. In addition to modulating the provision of protein / energy delivery, speakers looked at influence of nutrition on blood glucose control and discussed new clinical data suggesting that higher protein – lower carbohydrate enteral nutrition may improve glycaemic control without increasing the risk of hypoglycaemia.

Glycaemic control in critically ill patients: how tight should it be?

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There is still no widespread agreement around optimal targets for glucose control in the ICU: some clinicians maintain that glucose control is unnecessary and harmful, while others claim that blood glucose control is essential to improve prognosis.[1-3]

Those who favour liberal glycaemic control assert that hyperglycaemia is simply a beneficial adaptation in critically ill patients to provide fuel for vital organ systems. This view is supported by results from the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) study which concluded that tight glycaemic control (TGC) led to moderate and severe hypoglycaemia and an increased risk of death.[4]

The other view is that hyperglycaemia, in the context of early nutrition, is maladaptive and harmful. Glucose overload in cells that do not need insulin for glucose uptake may cause mitochondrial damage and, while hypoglycaemia is a risk, it can be prevented.

To explore the relationship between blood glucose levels and prognosis, we carried out two studies, using an identical design, on patients entering either the adult surgical ICU (S-ICU) or adult medical ICU (M-ICU).[5,6] In both studies, patients were randomly assigned to receive intensive insulin therapy (IIT: target maintenance level 80 to 100mg/dL) or conventional treatment (insulin only when blood glucose was between 180 and 215mg/dL and stopped again when falling below 180mg/dL). IV glucose was given on admission, followed on day 2 by early standardised parenteral (PN) combined with enteral nutrition (EN).

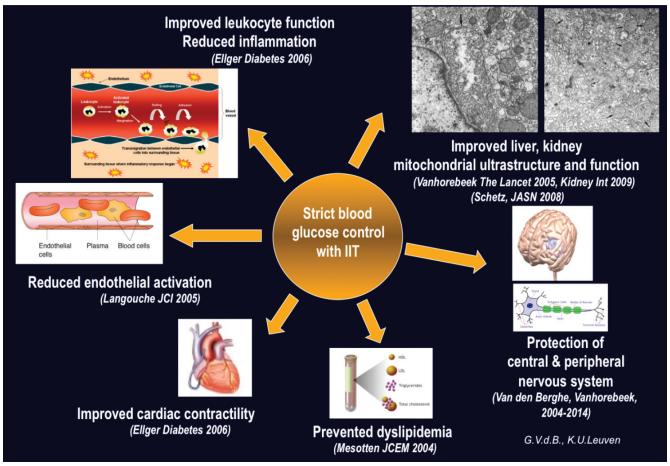
Pooling the results for the 2748 patients, IIT was associated with a clear reduction in hospital mortality of 4% (p=0.02) in the total population and 8% (p=0.006) among those patients who were in the ICU for at least 3 days.[7]

It was unclear whether maintenance of normoglycaemia or administration of insulin contributed to the clinical benefits but a subsequent animal study suggested that most benefits were due not to the administration of insulin but to the avoidance of hyperglycaemia.[8] Glycaemia-independent effects of insulin were evident only when normoglycaemia was maintained.

Further studies found that hyperglycaemia brought about cellular glucose overload in the kidney, which was associated with mitochondrial dysfunction and renal injury. Histological examination showed clear flattening of the tubules with loss of tubular epithelium and intraluminal debris or calcification in kidneys from the hyperglycaemia group.[9] It was also found that hyperglycaemia induced cellular glucose overload in the liver and myocardium, causing mitochondrial dysfunction.[10]

In 7/9 human patients who had been treated conventionally there were enlarged mitochondria in liver samples with increased abnormal and irregular cristae. Only 1/11 patients given intensive insulin therapy displayed these abnormalities (p=0.005).[11] The authors noted that the lack of effect on skeletal-muscle mitochondria suggested a direct effect of glucose toxicity rather than of insulinaemia.

Numerous mechanistic studies have confirmed that cells which are not dependent on insulin for glucose uptake can experience mitochondrial damage from hyperglycaemia in the context of critical illness.



A post hoc analysis of the results from the S-ICU and M-ICU studies found a marked survival benefit of intermediate vs limited control, and a slight further improvement with tight control, while only tight control produced very marked benefits in terms of new kidney injury.[5-7] With polyneuropathy, benefit was only seen with the tightest control.

In children, it is critical to target relevant age-adjusted values; targeting adult fasting levels of glucose may be harmful or, at best, ineffective. Seven hundred critically ill infants and children who were admitted to the paediatric ICU (PICU) were randomly assigned to target blood glucose levels (2.8 to 4.4mmol/L for infants, 3.9 to 5.6mmol/L for children) with insulin infusion throughout PICU stay, or to a second group where insulin infusion was used only to prevent blood glucose exceeding 11.9mmol/L.[12] BG was brought down to fasting levels in the intensive group and benefits of tight control were seen in multiple areas including shorter PICU stay (5.51 vs 6.15 days, p=0.017), lower C-reactive protein (9.75mg/L vs 8.97mg/L, p=0.007) and fewer infections (29.2% vs 36.8%, p=0.034). Hypoglycaemic episodes must be carefully managed to avoid rebound to high glucose levels. A comparison of children who had experienced hypoglycaemic episodes with those who had not, revealed no adverse effects on IQ, visual-motor integration or executive functions.

This contrasts with the findings of the NICE-SUGAR study which reported an increased risk of death in ICU patients who had experienced a hypoglycaemic episode.[4] This was attributed not to any effect on organ function, rather to cardiovascular failure.

Several important differences between the studies need to be highlighted. First, different target levels were used, with the two study arms in the NICE-SUGAR study being much closer together. Compliance levels also differed: in the Leuven studies, 70% of patients in the intervention group achieved target levels compared to less than 50% in the NICE-SUGAR study.

Many of the glucometers allowed in the NICE-SUGAR study have since been found to be unsuitable for their purpose.[13,14] Inaccuracies in measuring glucose can result in poor insulin titration and lead to large BG fluctuations and undiagnosed hypoglycaemia. Further errors could have been introduced through use of a too simple "if-then" algorithm that could be adapted or even set aside, unlike the computerised algorithm that has been developed at Leuven.[15]

Finally, in the NICE-SUGAR study, feeding was almost entirely via the enteral route whereas at Leuven, inadequate enteral feeding was supplemented with PN. It is possible that the NICE-SUGAR feeding protocol induced global substrate deficit through insulin-induced suppression of metabolism. On the other hand, PN in the Leuven studies may have increased the severity of stress-induced hyperglycaemia, with insulin infusion being required to counter the effect.

To investigate this, two RCTs were conducted to compare early vs late PN in critically ill adults (EPaNIC) and children (PEPaNIC).[16,17] Both studies produced similar results, more pronounced in children, with patients experiencing more infections and a lower likelihood for live discharge with early PN. In a secondary analysis it was found that delayed recovery with early feeding was explained by the amount of proteins or amino acids consumed, rather than glucose.[18] The likely mechanism is that amino acids suppress autophagy, a process which eliminates mitochondria that are damaged by hyperglycaemia.

Given these insights, our proposal is to re-do our original randomised controlled studies but under different conditions. In particular we will target fasting blood levels against hyperglycaemia up to 215mg/dL, and will not include early PN. This study, the "TGC-fast" study has received funding and is now in the process of being set up to recruit almost 10,000 patients.

Dysglycaemia in the critically ill

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As has been pointed out, the benefits of tight glycaemic control in the ICU have by no means been clearly established or accepted. In 2010 a meta-analysis of seven prospective randomised studies concluded that intensive insulin therapy in mixed ICU patients was not supported by evidence.[19]

Today we understand that hyperglycaemia, hypoglycaemia, and high glycaemic variability are all associated with poor outcomes. A review of 44 studies in the literature reporting hyperglycaemia in over 500,000 ICU patients found an association with many different types of outcomes. Another study on a large database of more than 100,000 patients, demonstrated that hyperglycaemia, hypoglycaemia, and high glycaemic variability all increased the risk of in-hospital mortality.[20]

Another large multi-centre study in 45,000 ICU patients found that while hyperglycaemia, hypoglycaemia, and high glycaemic variability were each independently associated with mortality, diabetic status modulated these relations such that patients with diabetes may benefit from higher target glucose ranges than those without diabetes.[21]

What therefore is the best way to manage blood glucose in the ICU?

The digestion and absorption of carbohydrates is a complex sequence of events starting in the mouth with amylase, which breaks starches down into shorter-chain sugars. Dextrins and sucrose are broken down further by specific enzymes, while other enzymes (lactase and maltase) at the brush border of the gut contribute to the breakdown of lactose and the oligosaccharides. The end result is glucose, which passes into cells and is released into the bloodstream.

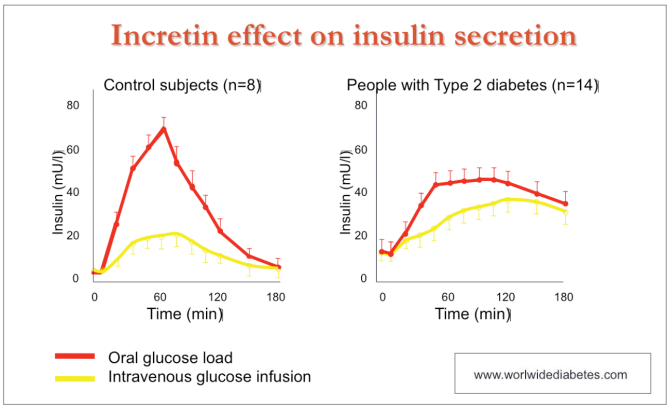
The different types of dietary carbohydrate, such as monosaccharides, oligosaccharides, or polysaccharides, differ in their speed of absorption. The "glycaemic index" is used as a convenient classification to categorise the speed of absorption.

Regarding enteral nutrition, some diabetes-specific formulas (DSF) are available, which are characterised by a lower percentage of carbohydrates and a higher percentage of lipids than standard formulas. However, rather than the amount of carbohydrate, the key difference is the type of carbohydrate as the formulations are put together to give a lower glycaemic index for the diabetes-specific formulas.

A systematic review of the literature in this area included RCTs which compared DSFs with standard formulas, finding that DSF was more effective in controlling glucose profiles. The requirement for insulin in patients with diabetes was lower when using these DSFs.[22] The authors speculated that this may be due to the type of carbohydrate used in these formulations, which may be more slowly digested and absorbed than in standard formulas.

There are not many studies on the role of DSF in the ICU. A small study of DSF in hyperglycaemic, mechanically ventilated, critically ill patients assigned around 50 patients to each of three groups, two of which used DSFs while the third used a standard control formula.[23] Insulin requirements were lower in the two DSF groups, while glycaemic control was significantly better.

An important physiological issue that we have to consider in feeding critically ill patients is the incretin effect. Following oral feeding, hormones released by the GI tract will stimulate the pancreas to release insulin. In healthy, non-diabetic subjects, administration of glucose by the IV rather than oral route results in the stimulation of much lower quantities of insulin, as the gut hormones are not produced in the same quantities. In diabetic patients, there is very little difference between the two routes of administration.



A meta-analysis of 13 studies examining the influence of enteral vs parenteral nutrition on glucose control in patients with acute pancreatitis confirmed that PN was associated with an increased risk of hyperglycaemia and therefore an increased requirement for insulin.[24]

In patients receiving continuous enteral feeding, if this is associated with a release of endogenous insulin then the amount of exogenous insulin needed to maintain a steady blood glucose level would be lower during feeding and higher during interruptions. Hence, the calculated insulin sensitivity would fall when feeding is interrupted and rise when feeding is restarted.

This hypothesis was tested in a group of critically ill, non-diabetic patients for whom records were available, for a minimum of 10 hours of enteral feeding followed by at least 7 hours with an interruption to enteral feeding, and at least 5 hours of resumed EN.[25] Data for 52 of these patients was available and it was found that insulin sensitivity dropped following interruptions to enteral feeding, thereby supporting the presence of an incretin effect.

New guidelines for glucose control were published in 2010 just after the controversy between the Leuven studies and the NICE-SUGAR study.[26] Unfortunately these guidelines reflect the uncertainty and lack of evidence: regarding carbohydrate intake it is not possible to suggest a general recommendation of maximal or minimal amounts of intravenous or enteral carbohydrates to be administered to critically ill patients regardless of the type, the severity of the pathology and the delay from onset of disease. It is also suggested that hyperglycaemia be reduced by restricting intravenous glucose in critically ill patients.

A pragmatic approach is to begin EN as soon as possible, adapting the infusion rate to the tolerance of the patient, trying to limit caloric debt rather than to achieve full matching of energy expenditure. In some centres, routine clinical practice includes the administration of low doses of IV glucose (50-100g/day) as a maintenance solution. As well as this, the use of dynamic scales for the dosing of insulin and attempts to minimise glycaemic variability are strongly recommended.

Facilitated glucose control in the ICU through nutrition

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As recently as 2010, the view of metabolic requirements for patients admitted to ICU was that all patients had the same metabolic needs and could therefore be managed with the same nutritional product. In general, critically ill patients were fed along the same lines as healthy people in the ratio of around 50% carbohydrates, 35% lipids and 15% protein. However, little benefit has been found from this approach or from the strategy of "temporary starvation" to patients in the ICU who cannot otherwise feed.

During starvation, protein is often used as an energy source rather than as an anabolic precursor to muscle synthesis. In the absence of glucose there is a lack of substrate for the formation of pyruvate, which leads to a decrease in the uptake of protein into tissues. Instead dietary proteins are broken down into amino acids to provide an alternative energy source. The goal of medical nutrition therapy in the critically ill is to maximise anabolism, minimise catabolism and minimise oxidation of amino acids.

The way in which patients are fed can have an impact on sugar levels and insulin infusion rates. In the EDEN study, 1000 adults with acute lung injury requiring mechanical ventilation were randomised to receive either trophic or full enteral feeding for the first 6 days.[27] Although the feeding strategy had little effect on mortality, infectious complications and ventilator-free days, the trophic group had lower plasma glucose levels and required lower insulin infusion rates to achieve BG targets.

While energy feeding in critically ill patients has been well studied, until recently little was known about early protein feeding. Insights were provided by a 2014 observational study with 843 mixed medical-surgical critically ill patients who required prolonged mechanical ventilation.[28] Food intake and energy expenditure were closely monitored over four days. It was found that in non-septic, critically ill patients, early high protein intake was associated with lower mortality, and early energy over-feeding with higher mortality. In septic patients, early high protein intake had no beneficial effect on mortality.

The first study to investigate the concept of permissive underfeeding evaluated the effect of restricting non-protein calories compared to standard enteral feeding in 894 critically ill adults while maintaining the full recommended amount of protein in both groups.[29] There was no difference in any of the many clinical outcomes that were measured such as mortality, days free from mechanical ventilation, length of ICU stay and length of hospital stay.

We have recently completed a study, as yet unpublished, to determine whether blood glucose control could be facilitated by using an enteral nutrition formula containing a low level of carbohydrates, lower medium chain triglycerides, and very high levels of hydrolysed whey protein, to ensure optimal protein delivery. The DIVINE study was an open label multi-centre randomised trial carried out at seven academic medical centres in the USA. It was planned to enrol 280 patients with the aim of 160 completing five days of enteral nutrition. The study ran for almost two years, from August 2014 through July 2016.

Patients were included if they were mechanically ventilated, critically ill, obese or overweight (BMI 26 to 45), and required enteral nutrition for at least five days. Patients were excluded if they had liver failure, trauma or were planned for major surgery.

A control group was fed a high protein formula with regular amounts of carbohydrate, and the intervention group had a very high protein, low carbohydrate formula.

DIVINE: Intervention

- **Control group**: High protein formula
- **Experimental group**: Very high protein, low carbohydrate formula

	Control Group (Replete®)	Experimental Group (Peptamen® Intense VHP)
Caloric Density (kcal/mL)	1.0	1.0
Protein (% energy)	64 g/L (25%)	92 g/L (37%)
Carbohydrate (% energy)	112 g/L (45%)	76 g/L (29%)
Fat (% energy)	34 g/L (30%)	38 g/L (34%)

Both feeds had a caloric density of about 1kcal/ml, but the protein in the experimental group was about 50% higher at 92g/L while the carbohydrates were about a third lower at 76g/L, and the fat content was fairly similar in both groups at 38 and 34g/L. The aim was to deliver 1.5g/kg of ideal body weight per day of protein.

The primary endpoint was the rate of glycaemic events in the first seven ICU days as defined by blood glucose levels outside the interval of 6.1 to 8.3mmol/L. Secondary endpoints included blood glucose, markers of nutritional status, urine and serum ketones, insulin and dextrose administered, and clinical outcomes.

One hundred and five patients were randomised (53 control and 52 experimental) and 102 were included in the intention to treat (ITT) analysis. There were 51 patients in each arm. The groups were similar apart from a greater number of women in the control group.

Regarding nutritional intake, the experimental group received significantly fewer calories and carbohydrates than the control group as planned, and both groups received about the same amount of protein. Over the seven days of the study, caloric intake was about 60% of the planned intake in both groups, and slightly more than 60% of the protein target, which was 1.2g/kg compared to the target of 1.5g/kg.

Looking at the primary endpoint, there was no difference between the groups in the rate of glycaemic events outside of the intervals (6.1 to 8.3mmol/L). In the experimental group there was a higher rate of glycaemic events in the normal range of 4.4 to 6.1mmol/L but these are not defined as hypoglycaemic. In the same group there was a lower rate of marked hyperglycaemia (>8.3mmol/L). The mean glucose was lower in the experimental group by almost 1mmol/L (p=0.004). There was no difference in the rates of hypoglycaemia (<4.4mmol/L), and there was a smaller glycaemic dispersion in the experimental group (p=0.0015). There was a significant decrease of 11% in the frequency of insulin administration in the experimental group and there was no difference in the amount of rescue dextrose that had to be used.

There was an increased frequency of abdominal distension in the experimental group, which may have been due to the formula and to intolerance of higher protein levels. Distension was considered to be related to the formula in one case in the control group and one in the experimental, which was withdrawn from one patient. Overall there was no difference between groups in the number of patients with adverse events. Mortality was not significantly different, but was numerically lower in the experimental group with two deaths (4%) compared to six (12%).

To conclude, in the DIVINE study a very high hydrolysed whey protein and low carbohydrate formula facilitated blood glucose control in critically overweight and obese patients. Although the formula did not reduce the incidence of blood sugar events outside the interval of 6.1 to 8.3mmol/L, it did lower the dispersion of blood glucose, resulted in a lower incidence of hyperglycaemia (>8.3mmol/L), increased the incidence of normoglycaemia and decreased insulin use without increased adverse events.

The increased recognition of proteins in critical illness

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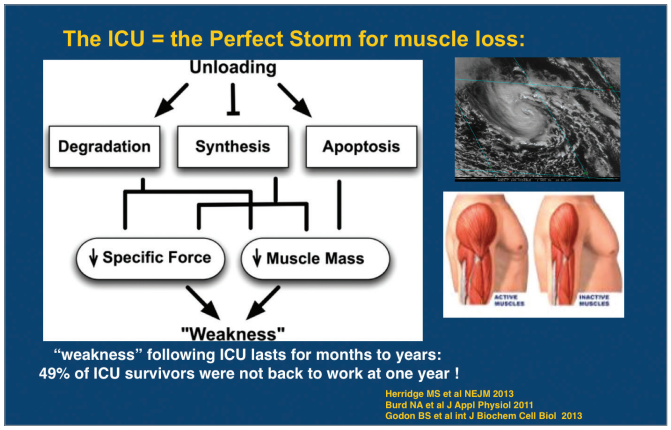
There are many new concepts and old controversies surrounding nutrition in critical care such as: the role of trophic feeding, permissive underfeeding, the use of immune modulating agents, and the optimal timing of nutrient delivery. However, enteral nutrition and protein delivery have consistently been found to be beneficial.

Traditionally, the concerns in the ICU were about meeting energy requirements while protein levels were rarely considered. Early work carried out in the 1920s by Cuthbertson had largely been forgotten until the 1980s.

Conditions in the ICU result in loss of muscle mass: patients are immobile, often have minimal energy and protein delivery, and undergo little or no resistance exercise.[30-32] Twenty-one days after a single blunt injury, 16% of total body protein is lost, 67% of it from the muscle.[33] Resting energy expenditure (REE) increases progressively over the first week to 40% above normal and can still be elevated after three weeks.



Conventional methods of analysis may not give a true picture of the rate of muscle loss. Ultrasound of the rectus femoris muscle in ICU patients showed a loss of around 10% within 10 days; but biopsies showed a thinning of muscle collagen fibres by 17.5% and when using a ratio of DNA to cellular protein, a loss of 29.5% is seen.[34] Significant inflammatory changes in skeletal muscle were observed despite patients being given an average of 0.7g/kg/day of protein.

Muscle loss is not confined to extremity skeletal muscle. A study investigating muscular volumetric changes compared the diaphragm to extremity skeletal muscle and found that there was greater loss of the diaphragm muscle.[35]

A recent study investigating mechanisms of chronic muscle wasting in elderly ICU patients found that most parameters such as proteolysis, autophagy and inflammatory cells normalised at six months, but satellite cells remained consistently depressed.[36] Satellite cells appear to regulate the ability of muscle to recover from major loss, therefore if these cells are compromised, there is a decreased ability to regenerate muscle. ICU-acquired weakness and muscle wasting has a complex aetiology but increased protein degradation, reduced protein synthesis and often limited protein intake play a part.[37]

The loss of muscle mass is dramatically increased on admission to an ICU. If inadequate protein is not supplied to these catabolic patients muscle lost during hospitalisation may never be regained. It has been reported that short term amino acid infusions improve protein balance and small randomised clinical trials with parenteral nutrition show modest benefits in muscle strength and fatigue.[38-41]

Questions still surround the optimal target for protein. There are numerous studies supporting protein delivery in the ICU from 0.8g/kg/day up to 2.5g/kg/day. Large observational studies of ICU patients report most critically ill patients receive around 0.6g/kg/day of protein. Several studies consistently support that the goal for protein delivery should be at least 1.5g/kg/day and possibly higher.[41-45]

There is no consensus as yet on the upper limit. Some clinicians advocate delivery of up to 3g/kg/day (in adolescent patients), but guidelines are generally consistent in recommending an upper limit of 2.5g/kg/day.[46,47] There are potential issues with excess protein including azotaemia, hepatic protein synthesis and altered mental status which are more theoretical than observed.[48,49]

A number of studies have demonstrated that infusion of exogenous amino acids can improve whole-body protein balance, without increasing amino acid oxidation rates in critically ill patients.[38,50,51] A higher protein intake was generally associated with an improved nitrogen balance, with dosages of 2g/kg/day being more successful than lower intakes.[52]

There is also concern that protein delivery may affect the autophagy balance. Nutrient delivery inhibits autophagy but activates cellular protein synthesis so there is not a simple direct relationship between feeding (or starvation) and autophagy.

Could anabolic resistance be a factor in ICU patients? Anabolic resistance is driven by an insensitivity to the anabolic effects of amino acids, particularly leucine. Although we do not have definitive answers for overcoming anabolic resistance we do know that certain approaches, such as hypercaloric PN or EN, hypocaloric feeding, use of anti-inflammatory, and appetite stimulants do not work.

On the other hand we know that certain interventions work consistently to protect lean body mass: protein supplementation, delivered by pulsed bolus; early enteral feeding, which protects the gut barrier and decreases systemic inflammation; metabolic modulation with nutrients such as leucine, arginine, and specialised pro-resolving molecules (SPMs); glycaemic control, resistance exercise and support for the microbiome. Other interventions appear to work in other patient groups but have not yet been confirmed as of benefit in the ICU.

In conclusion, there is good evidence to support protein in the ICU is beneficial although delivery must be individualised. An upper range of 2.5g/kg/day is considered safe. Optimal protein intake may be different in the acute compared to the prolonged phase of illness. Due to the heterogeneous nature of the ICU population decisions must be made on an individual basis. Aggressive protein delivery combined with resistance exercise may improve muscle kinetics, metabolism and regeneration. Most of our evidence currently comes from observational trials, which may not be consistent with RCTs and there are still many unanswered questions.

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