

Interleukin 6 (IL6): Ultimate Muscle Fat Burnerâ€™ Friend or Foe?

Contributed by By Dan Gwartney, MD
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The body uses chemical messengers to communicate between the various tissues in order to meet the energy needs of the body, facilitate development and address the demands of the environment. Most people are familiar with this concept through their understanding of endocrine hormones, such as testosterone, growth hormone or insulin. There are many other messenger chemicals present in the body…some familiar, some strange and exotic sounding. Neurotransmitters travel from nerve to nerve in the brain or the body. Similarly, many cells release paracrine and autocrine hormones that are rarely spoken of outside of science journals or research labs.

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Endocrine hormones travel through the bloodstream to affect tissues distant from where they were produced. Paracrine and autocrine hormones stimulate receptors on cells located nearby, even stimulating the same cell in the case of autocrine hormones. A major class of hormones that seems to encompass properties of all three types of hormones is the cytokines. The number of known cytokines is fairly large and continues to grow as new discoveries are reported. One that is most well studied is called interleukin 6 or IL6.

Many cytokines are called interleukins because they are used by the immune system to stimulate inflammatory cells called leukocytes. However, as is being (slowly) understood by clinical scientists, most hormones are not tissue-specific. In other words, hormones do not affect just one tissue— for example, testosterone does not affect just skeletal muscle, but also the sex glands, skin, fat cells, blood cells, brain, heart, etc. This is also the case with IL6. However, IL6 differs from testosterone in one important way. Whereas testosterone is produced (primarily) only in the testes, IL6 is produced in a variety of tissues and cells.¹

While IL6 holds an important role in immune function, starting the inflammation response when bacteria are detected in the bloodstream and supporting the fever response, it is central to many, many other functions in the body. Bodybuilders and athletes don’t care about leukocytes, but they do care about muscle and fat. Now (over 300 words later) the article becomes interesting. The relationship between IL6 and obesity or conditions that might increase or decrease fat storage has been a confusing tale of conflicting science. Initially, IL6 was believed to be a pro-obesity factor, as it is increased in obese people and has been shown to increase insulin resistance in animal studies as well as lab studies using human tissue from certain organs.²⁻⁵ Yet, other studies have shown that IL6 increases the metabolism and fat burning.⁶⁻⁹ The whole issue is still so unresolved, as to have the leading experts in the field still debating on whether IL6 is a factor that aids or impairs aspects relating to weight management and metabolic health.^{10,11} Fortunately, as new information is released and scientists’ knowledge and experience expand, the role of IL6 in humans is becoming clearer. Unfortunately, only a few scientists are looking at the topic broadly enough to understand the effects of IL6 under a variety of human conditions. Rodents are often used as the experimental subjects in many studies because they are expendable, cheap, have short life spans and a physiology that resembles humans. Unfortunately, with the exception of attorneys and career politicians, rats and humans are different enough to make it difficult to compare the findings in one species to the other.¹⁰ Further, the conditions humans live in are extremely varied and often quite extreme. It is important to understand the impact of the subjects when trying to interpret the results of IL6 clinical studies. Lastly, it is

important to realize that because IL6 is involved in so many different systems in the body, that changes unrelated to fat loss/fat gain may affect IL6 levels.

Early on, it was believed that IL6 promoted fat gain and supported the condition of obesity, because IL6 levels are higher in obese people compared to lean people.¹² Obesity has been found to cause a condition of chronic (persistent or long-lasting) inflammation. Remember, IL6 plays a central role in inflammation, so it is not surprising to see that IL6 is increased during an inflammatory state (obesity). The inflammation exists in the intra-abdominal fat, especially the visceral fat that surrounds the intestines and other internal organs.¹³ High levels of visceral fat are closely associated with a number of poor health conditions, such as diabetes, cardiovascular disease and the Metabolic Syndrome. At first, this bit of evidence seems damning, suggesting IL6 is a pro-obesity factor. However, looking more closely at the role of IL6 in inflammation and later data finds this may be (and likely is) misleading. IL6 co-exists with another cytokine called tumor necrosis factor-alpha or TNF. TNF is released in high concentration by visceral fat cells (inside the abdomen) and reaches the liver in very high amounts. TNF is thought to be a causative factor in a number of negative cellular and metabolic effects, such as insulin resistance, type 2 diabetes and cardiovascular disease. TNF also stimulates the production of IL6.

Often, when a hormone stimulates the production of another hormone, it is doing so to generate a second signal or carry the effect of the first hormone into other cells. However, sometimes a second hormone is produced to regulate the first hormone in order to prevent an excess of the original signal. Yep, that was confusing. Think of testosterone, which actually reduces the release of LH (the pituitary hormone that stimulates testosterone production). This is called negative feedback. In humans, IL6 suppresses (reduces) TNF, an anti-inflammatory effect. Thus, it is clear that conditions that create high levels of TNF would also create high levels of IL6, which attempts to protect against the overproduction of TNF. Without understanding the relationship between these two cytokines, one would tend to blame the effects caused by TNF on IL6 as well, sort of a molecular guilt-by-association.

IL6 is known to cause some effects that on the face of things would seem to be obesigenic (promoting obesity). When IL6 interacts with receptors on liver cells, it stimulates enzymatic reactions that increase insulin resistance.^{3,5,14} During periods of fasting (not eating), the liver creates sugar by breaking down glycogen or from fatty acids or amino acids in a process called gluconeogenesis. When a person begins eating, one of the first responses of the body is for this process to be shut down in the liver, as the first phase of insulin is released during a meal. The shutdown of gluconeogenesis occurs because the constant efflux (outpouring) of sugar from the liver would strain sugar control mechanisms and force the body to maintain higher insulin levels longer, resulting in a pre-diabetic state. In fact, several of the latest diabetes drugs function by restoring this first phase response and result in significant weight loss for many people.¹⁵ The constant bombardment of the liver with TNF and IL6 from visceral fat likely creates a state of hepatic (liver) insulin resistance that accounts for some of the negative consequences seen in states with chronic low-level inflammation, such as obesity.

IL6 also produces insulin resistance in adipocytes (fat cells).⁴ Though this sounds bad, in regard to fat loss, it may be a good thing. Fat cells are necessary for long-term health, as they buffer the concentration of fatty acids in the bloodstream—during periods of starvation (which is associated with low insulin levels), fats are broken down and released; following a meal, when insulin is high, fats are stored. Recall that when the liver suffers from insulin resistance, it continues to pump out sugar, forcing insulin to rise. This increases the fat storage signal, which increases the fat mass, the source of TNF, which stimulates IL6 production. It is a vicious cycle, like metabolic poverty. When IL6 creates a state of insulin resistance in the fat cell, it prevents it from storing fat to the same degree, so it would seem that there would be a balance—a give and take. However, remember that the IL6 affecting the liver comes primarily from the visceral fat, whose blood supply drains directly into the liver; whereas the circulating IL6 in the bloodstream that interacts with all

other depots of fat is diluted by the greater volume of blood or generated by other tissue, such as skeletal muscle or by the fat cell itself.

This brings to the forefront one of the areas of confusion in the field of IL6 research, acute versus chronic effects. IL6 does indeed have some effects that can lead to insulin resistance and pre-diabetes, therefore promoting obesity if IL6 levels are mildly elevated long-term. However, in normal-weight people who do not have large depots of visceral fat, acute (short-term) spikes in IL6 actually appear to be beneficial. To better understand this, it is important to realize the impact of lifestyle—active versus sedentary.

Aside from fat cells and cells involved in immunity and inflammation, there is one other major source of IL6—contracting muscle.^{9,16,17} When skeletal muscle contracts, such as during exercise, IL6 is released in huge quantities. This IL6 acts on the tissue immediately surrounding the area as well as getting into the bloodstream. By the time it reaches the liver (through the hepatic circulation rather than the portal circulation which is the route taken by visceral fat-originated IL6), the IL6 is diluted. However, the levels reaching subcutaneous fat are considerable. Why would the body want to put out loads of IL6, especially during exercise when it needs to absorb energy, when IL6 has been shown to increase insulin resistance in the liver and fat cell?

During short-term exercise, people generally are not consuming calories, particularly people seeking to lose fat. Thus, there is a huge demand for sugar and fatty acids from the bloodstream to feed the working muscle, which can increase its metabolic needs by 40 times or more compared to the resting state (that is an increase in calorie burning of 4,000 percent!). In order to decrease the competition from other cells, it is beneficial to cause a temporary insulin resistance throughout the body in order to reduce the amount of sugar being taken up by other tissues and organs. Also, by keeping the insulin resistance of the liver higher, the liver continues to pump out sugar through the gluconeogenesis process. Further, as the fat cells are less responsive to insulin, they will break down and release more fatty acids into the bloodstream to meet longer term energy demands.

But what about the muscle? After all, it would do little good to increase insulin resistance everywhere only to have the working muscle suffer the same fate. Fortunately, the body has a wonderful interplay of systems. Glucose (sugar) from the blood is taken into muscle through transporters called GLUT4 transporters. In resting conditions, these transporters are held inside the muscle cell so that this large tissue mass does not rob the vital organs of energy. However, when insulin stimulates receptors on the muscle cell surface, the GLUT4 transporters rush to the cell membrane and start taking in their share of the calories provided by a meal.¹⁸ Obviously, if there is an excess of IL6, this mechanism would seem to function poorly and sugar control would be affected throughout the whole body.¹⁹ This is the case seen in rodents. In contrast, studies in humans have shown the opposite, with insulin concentrations dropping and glucose getting shuttled into and burned for calories quicker, as well as an increase in fatty acid oxidation (calorie burning).^{20,21} In fact, some leading researchers believe the overall effect of IL6 is insulin sensitizing in humans.

This may sound like a wonderful condition, but prolonged exposure to IL6 would not necessarily be a positive situation. Remember, the fat cells have an important role in buffering fatty acid concentrations. Otherwise, negative effects such as insulin resistance and atherosclerosis become pathologic. Thus, it would seem that IL6 could be a very positive player if

its release was controlled and related to a situation where fat and sugar calories were burned quickly.

Sounds like exercise, doesn't it? Exactly so. An interesting observation was noted that contracting muscle generates a number of physiologic modifiers. Many people are familiar with lactic acid, but guess what other major factor is released during exercise by contracting muscle? That's right, IL6. Exercise is sometimes called a metabolic sink because it is a unique physiologic condition that is associated with a tremendous increase in the metabolism of the body in general and muscle in particular.⁸ One relevant effect of muscle contraction that is often not accounted for is the insulin-independent glucose uptake. When a muscle contracts, it causes GLUT4 transporters to migrate to the cell membrane so that the muscle can grab sugar from the bloodstream to use for energy, without needing to be stimulated by insulin.²² So, the working muscle is protected from any potential insulin resistance effect of IL6 during exercise. Remember, in humans IL6 is believed to increase insulin sensitivity in muscle, not insulin resistance, so its effect would be to enhance glucose uptake by exercising muscle.^{7,20}

One last observation made in humans that is particularly beneficial is that high concentrations of IL6 cause a significant increase in calorie burning, especially fatty acid oxidation (burning fat for energy).^{7,8,21,23} Thus, it becomes clear that in active individuals, IL6 plays a beneficial role in energy production and accounts for some of the fat-loss effect seen with exercise (increased metabolic rate, increased fatty acid oxidation and increased release of stored fat from fat cells). However, in a sedentary person, the IL6 source is not active muscle but visceral fat, which causes insulin resistance to a disproportionate degree in the liver, resulting in the continuous release of excess amounts of sugar and higher insulin levels. This promotes fat storage over the long term, as is seen in type 2 diabetics.

Researchers have looked at experimental conditions in which IL6 is elevated. Some have exposed people to proteins found in bacteria that cause fever...others have injected synthetic IL6-like drugs. In both settings, fat loss is increased. Not only does muscle-derived IL6 have a net fat loss effect, but it also seems to aid in muscle growth. IL6 is a vital factor for the satellite cells to differentiate (mature) into myofibers, which is an early step in muscle hypertrophy (growth).²⁴ However, this is only the case when IL6 is elevated in exercised muscle. Having systemically high IL6 levels, such as would be seen in obesity or during a fever, leads to muscle wasting. It has also been shown that natural testosterone levels are inversely related to chronic IL6 levels (meaning when testosterone is high, IL6 is low).²⁵ Also, TNF increases with age, causing IL6 to increase as well, and higher levels of these two cytokines are associated with a higher risk of poor health or death.²⁶ It remains to be seen what direction the field of research into cytokines will take, but one thing is clear amid all the confusion. Cytokines are not a simple set of hormones and the environment must be taken into account in order to understand their relative benefits and risks. It is possible that direct injections of IL6 into an exercised muscle or some method to upregulate IL6 production during exercise may increase the lipolytic effect of exercise, but there is no research yet to support that assumption. It is clear that chronically high levels of IL6, as opposed to acute elevations seen with exercise, are unhealthy and often reflect conditions that will lead to problems in the long run.

Nature did not intend for mankind to be sedentary and the duality of IL6 is a perfect example of a beneficial system that can cause problems in an unhealthy environment. Working the muscles intensely is a natural way to promote quicker fat loss and continuous muscle growth and IL6 appears to be one of the exercise-dependent factors responsible for many of the benefits of developing muscle mass and working out intensely.

So, is IL6 a friend or foe? The answer can be yes to both; IL6 is a friend to the fit and foe to the fat. Stay lean and work hard to keep this powerful hormone as an ally against obesity, aging and metabolic disease.⁸

SIDEBAR

Key Facts Relating To IL6 During Exercise And Fat Loss:

- • Resting IL6 comes from the visceral fat and is a sign of ongoing inflammation.
- • Resting IL6 causes insulin resistance in the liver and can promote dangerous health conditions.
- • Resting IL6 levels are three times higher in obese (BMI>30) compared to normal-weight people, four times higher in the super-obese (BMI>40).
- • In addition to inflammatory cells and fat cells, skeletal muscle is a major source of IL6.
- • A lifestyle that includes exercise lowers resting IL6.
- • During exercise, muscle contractions lead to the production/release of IL6, increasing blood levels nearly 100-fold. This is rapidly cleared once exercise ends.
- • Niacin and high-carbohydrate drinks during exercise lower the IL6 response to exercise in muscle.
- • A low-carbohydrate diet may allow for a greater IL6 response by keeping muscle glycogen levels low.
- • Supplementation with antioxidants may lower IL6 production during exercise.
- • Exercise-related IL6 acts as an anti-insulin at the liver and fat cell to increase energy substrate (fat and sugar) to the working muscle. This leads to fat loss.
- • Exercise-related IL6 works with insulin at the working muscle to increase sugar intake from the blood.
- • Exercise-related IL6 increases calorie burning in muscle and fatty acid oxidation specifically.
- • Exercise-related IL6 promotes the recruitment of satellite cells into muscle cells to promote muscle hypertrophy.
- • Low testosterone is associated with high IL6, aging and chronic diseases.

References:

1. van Snick J. Interleukin-6: an overview. *Annu Rev Immunol*, 1990;8:253-78.
2. Klover PJ, Timmers TA, et al. Chronic exposure to interleukin-6 causes hepatic insulin resistance in mice. *Diabetes*, 2003;52:2784-9.
3. Senn JJ, Klover PJ, et al. Interleukin-6 induces cellular insulin resistance in hepatocytes. *Diabetes*, 2002;51:3391-9.
4. Rotter V, Nagaev I, et al. Interleukin-6 (IL-6) induces insulin resistance in 3T3-L1 adipocytes and is, like IL-8 and tumor necrosis factor-alpha, overexpressed in human fat cells from insulin-resistant subjects. *J Biol Chem*, 2003;278:45777-84.
5. Senn JJ, Klover PJ, et al. Suppressor of cytokine signaling-3 (SOCS-3), a potential mediator of interleukin-6-dependent insulin resistance in hepatocytes. *J Biol Chem*, 2003;278:13740-6.

6. Carey AL, Steinberg GR, et al. Interleukin-6 increases insulin-stimulated glucose disposal in humans and glucose uptake and fatty acid oxidation in vitro via AMP-activated protein kinase. *Diabetes*, 2006;55:2688-97.
7. Al Khalili L, Bouzakri K, et al. Signaling specificity of interleukin-6 action on glucose and lipid metabolism in skeletal muscle. *Mol Endocrinol*, 2006;20:3364-75.
8. Glund S, Krook A. Role of interleukin-6 signaling in glucose and lipid metabolism. *Acta Physiol*, 2008;192:37-48.
9. Pedersen BK, Fischer CP. Physiological roles of muscle-derived interleukin-6 in response to exercise. *Curr Opin Clin Nutr Metab Care*, 2007;10:265-71.
10. Pedersen BK, Febbraio MA. Point: Interleukin-6 does have a beneficial role in insulin sensitivity and glucose homeostasis. *J Appl Physiol*, 2007;102:814-9.
11. Mooney RA. Counterpoint: Interleukin-6 does not have a beneficial role in insulin sensitivity and glucose homeostasis. *J Appl Physiol*, 2007;102:814-9.
12. Bastard JP, Maachi M, et al. Recent advances in the relationship between obesity, inflammation, and insulin resistance. *Eur Cytokine Netw* 2006;17:4-12.
13. Hamdy O, Porramatikul S, et al. Metabolic obesity: the paradox between visceral and subcutaneous fat. *Curr Diabet Rev*, 2006;2:367-73.
14. Kim JH, Kim JE, et al. Regulation of interleukin-6-induced hepatic insulin resistance by mammalian target of rapamycin through the STAT3-SOCS3 pathway. *J Biol Chem*, 2008;283:708-15.
15. Barnett A. Exenatide. *Expert Opin Pharmacother*, 2007;8:2593-608.
16. Pedersen BK, Steensberg A, et al. Searching for the exercise factor: is IL-6 a candidate? *J Muscle Res Cell Motil*, 2003;24:113-9.
17. Pedersen BK, Akerstrom TC, et al. Role of myokines in exercise and metabolism. *J Appl Physiol*, 2007;103:1093-8.
18. Huang S, Czech MP. The GLUT4 glucose transporter. *Cell Metab*, 2007;5:237-52.
19. Kim HJ, Higashimori T, et al. Differential effects of interleukin-6 and -10 on skeletal muscle and liver insulin action in vivo. *Diabetes*, 2004;53:1060-67.

20. Carey AL, Steinberg GR, et al. IL-6 increases insulin stimulated glucose disposal in humans and glucose uptake and fatty acid oxidation in vitro via AMPK. *Diabetes*, 2006;55:2688-97.

21. Petersen EW, Carey AL, et al. Acute IL-6 treatment increases fatty acid turnover in elderly humans in vivo and in tissue culture in vitro: evidence that IL-6 acts independently of lipolytic hormones. *Am J Physiol Endocrinol Metab*, 2005;288:E155-62.

22. Jessen N, Goodyear LJ. Contraction signaling to glucose transport in skeletal muscle. *J Appl Physiol*, 2005;99:330-7.

23. Hoene M, Weigert C. The role of interleukin-6 in insulin resistance, body fat distribution and energy balance. *Obes Rev*, 2008;9:20-9.

24. Serrano AL, Baeza-Raja B, et al. Interleukin-6 is an essential regulator of satellite cell-mediated skeletal muscle hypertrophy. *Cell Metabolism*, 2008;7:33-44.

25. Kapoor D, Clarke S, et al. The effect of testosterone replacement therapy on adipocytokines and C-reactive protein in hypogonadal men with type 2 diabetes. *Eur J Endocrinol*, 2007;156:595-602.

26. Maggio M, Guralnik JM, et al. Interleukin-6 in aging and chronic disease: a magnificent pathway. *J Gerontol*, 2006;61A:575-84.