InnoSlim®

For weight and metabolic support
through reduced glucose absorption in the intestine
increased glucose absorption in muscle and fat cells
reduced fat accumulation and inflammation in fat cells
reduced insulin resistance

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18 *in-vitro*, 2 *in-vivo*, 1 human study

Published in Journal of Agricultural and Food Chemistry (2007 & 2010)
Molecular Pharmacology
Adaptive Medicine

NPN 80089461

Pennies per serving

GRAS Affirmed
GENERALLY RECOGNIZED AS SAFE

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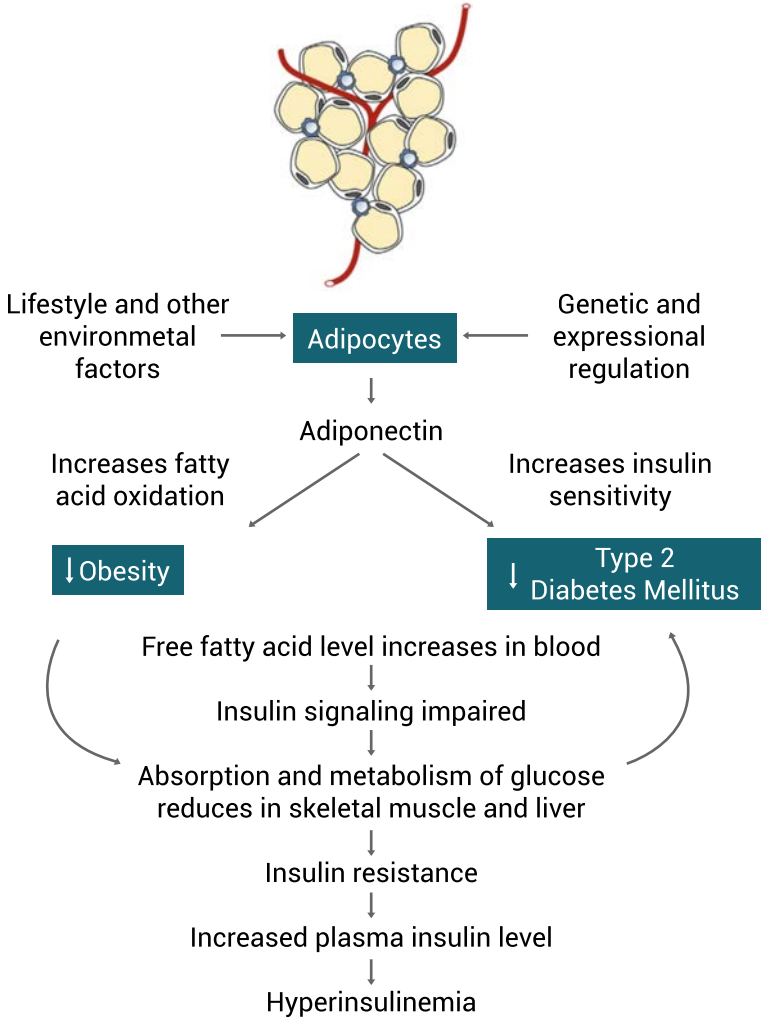
WHAT CAUSES METABOLIC SYNDROME

AND HOW ENZYMES AND PROTEIN, ADIPONECTIN, AMPK, GLUT4, SGLT1, ACC-P, HIF-1, PAI-1, RBP4, AND TNFα PLAY A ROLE IN THIS

It is well understood that excess carbohydrate and fat intake increases fat accumulation in our body and leads to weight gain, diabetes, high triglycerides and cholesterol. Research has shown that overweight, obese or diabetic persons are not able to effeciently breakdown their body fat due to low adiponectin in their blood plasma (7). Adiponectin is a protein hormone that activates the enzymes Adenosine Monophosphate-Activated Protein Kinase (AMPK), Acetyl Coenzyme A Carboxylase phosphorylation (ACC-P), Hypoxia Inducible Factor 1 (HIF-1) and GLUT4 transporters in our body to regulate glucose and fat metabolism in blood, muscle, fat cells, and liver (4, 8).

It is still unknown why overweight, obese or diabetic persons have low adiponectin. One research indicates it may be related to insulin resistance, high triglycerides and fat droplets in the muscle (9). Low grade chronic inflammation, such as expressed in our body by several inflammatory biomarkers Plasminogen activator inhibitor-1 (PAI-1), Retinol binding protein 4 (RBP4) and Tumor necrosis factor-α (TNFa) in fat cells have been linked to low adiponectin and insulin resistance (10).



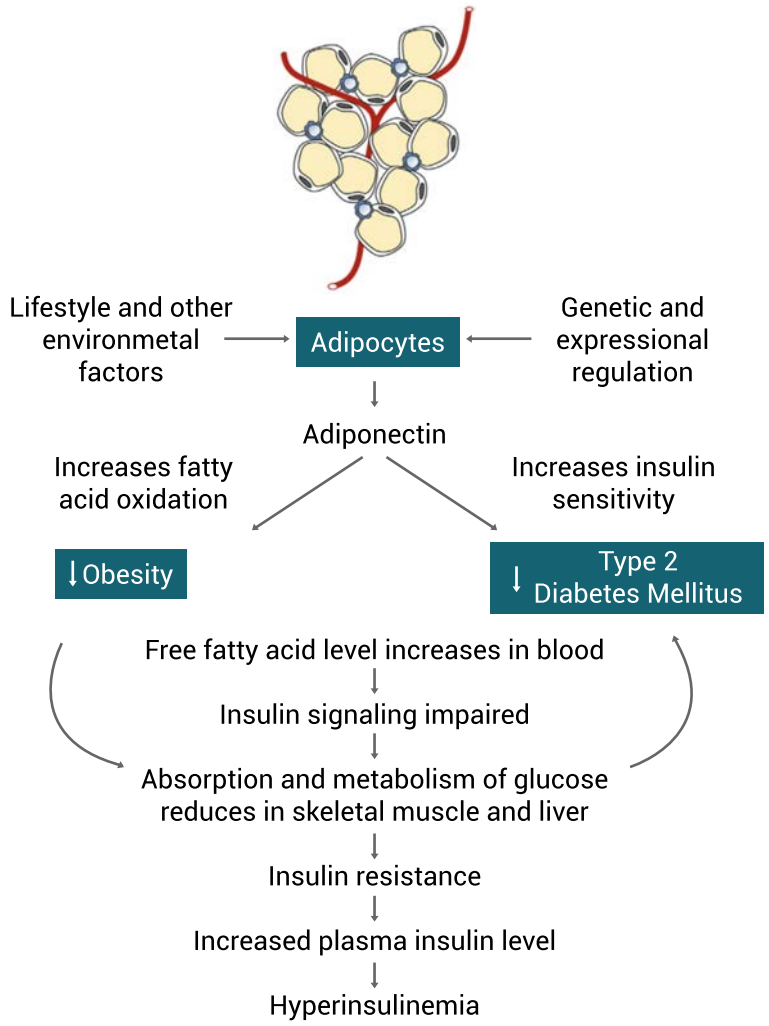
A BRIEF OVERVIEW ON ADIPONECTIN, AMPK, GLUT4, SGLT1, ACC-P, HIF-1, PAI-1, RBP4, AND TNFα

Adiponectin is a protein hormone that regulates glucose levels and fatty acid oxidation. Increased adiponectin decreases fat cell formation and increases energy expenditure. Adiponectin plays a role in the suppression of obesity, type 2 diabetes, and atherosclerosis.

Adenosine monophosphate-activated protein kinase (AMPK) is an enzyme that plays a role in cellular energy homeostasis. AMPK activation simulates hepatic fatty acid oxidation, ketogenesis, skeletal muscle fatty acid oxidation and glucose uptake, inhibits cholesterol and triglyceride synthesis, lipogenesis, and modulation of insulin secretion by pancreatic beta-cells.

Glucose transporter type 4 (GLUT4) is an insulin-regulated glucose transporter found primarily in adipose tissues and skeletal and cardiac muscles. Increased GLUT4 levels increases the absorption of glucose in muscles and decreases circulating glucose in blood stream.

Acetyl-CoA carboxylase (ACC) is an enzyme that regulates the metabolism of fatty acids derived from carbohydrates. Inhibition or deactivation of ACC phosphorylation (ACC-P) reduces fatty acids formation.

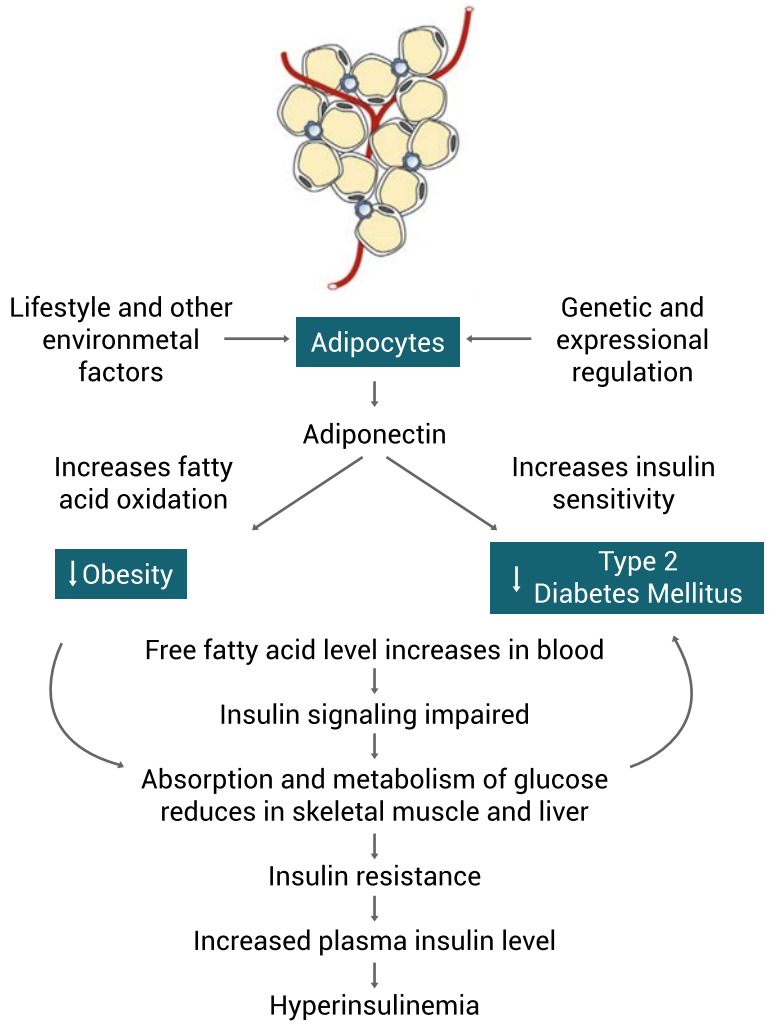


A BRIEF OVERVIEW ON ADIPONECTIN, AMPK, GLUT4, SGLT1, ACC-P, HIF-1, PAI-1, RBP4, AND TNFα

Hypoxia-inducible factor 1 (HIF-1), a transcription factor, is critical for systemic homeostasis to microenvironmental stimuli, e.g. hypoxia and low energy. Activation of HIF-1 has a positive effect on the glycolysis process, oxygen and energy homeostasis.

Sodium-glucose cotransporter 1 (SGLT1) transports glucose and galactose across the luminal (gut) side of enterocytes, and is the first step in the absorption of sugars from nutrients.

Plasminogen activator inhibitor-1 (PAI-1) is significantly induced in insulin resistant, diabetes and metabolic syndrome; **Retinol binding protein 4 (RBP4)**, expressed and secreted by adipose tissue, is strongly associated with insulin resistance; and **Tumor necrosis factor-α (TNFα)** in fat cells. As adipose tissue expands during obesity, there is an increase in inflammatory cytokines and a reduction in anti-inflammatory cytokines such as adiponectin, which contributes to local and systemic inflammation and disturbances in glucose homeostasis.



DISCOVER INNOSLIM®

InnoSlim® is NuLiv Science's proprietary metabolic nutraceutical composed of highly purified and fractionated *Panax notoginseng* and *Astragalus membranaceus* produced by a proprietary pharmaceutical extraction and processing technology.

InnoSlim® has shown in 18 *in-vitro*, two *in-vivo* and one human clinical study published in Journal Agricultural Food Chemistry, Molecular Pharmacology and Adoptive Medicine to regulate glucose and fat metabolism in Caco-2, fat and muscle cells by activating the master energy switch Adiponectin and AMPK. These activations lead to decreased glucose absorption in the intestine, increased glucose absorption in muscle and fat cells and decreased fatty acids formation and inflammation in fat cells (1, 2, 3, 5, 8, 10). Specifically, InnoSlim®:

- increases adiponectin in normal cells by 103% and insulin-resistant cells by 248%
- increases AMPK expression levels in muscles by 52% and fat cells by 300%
- increases GLUT4 expression level in muscle by 46% and fat cells by 488%
- increases glucose absorption in muscles by 50%
- increases glucose absorption in fat cells by 68% and fatty acid breakdown by 100%
- decreases glucose absorption in Caco-2 cells by 41%
- decreases glucose levels in rats by 11%
- increases insulin sensitivity in rats by 38%
- reduces inflammatory bio markers PAI-1 by 11%, RBP4 by 31% and TNFα by 61% in normal cells
- reduces inflammatory bio markers PAI-1 by 53%, RBP4 by 67% and TNFα by 38% in insulin-resistant cells
- increases ATP production in liver cells by 22%

DISCOVER INNOSLIM®

Excess circulating blood glucose is stored as fat and prolonged excess blood glucose leads to insulin resistance and more fat accumulation. InnoSlim® decreases glucose absorption in the intestine by reducing the glucose transporter SGLT1 and increases glucose absorption muscle and fat cells by increasing glucose transport protein GLUT4. These effects reduce circulating blood glucose and fat accumulation (1, 2, 3, 5, 8, 10).

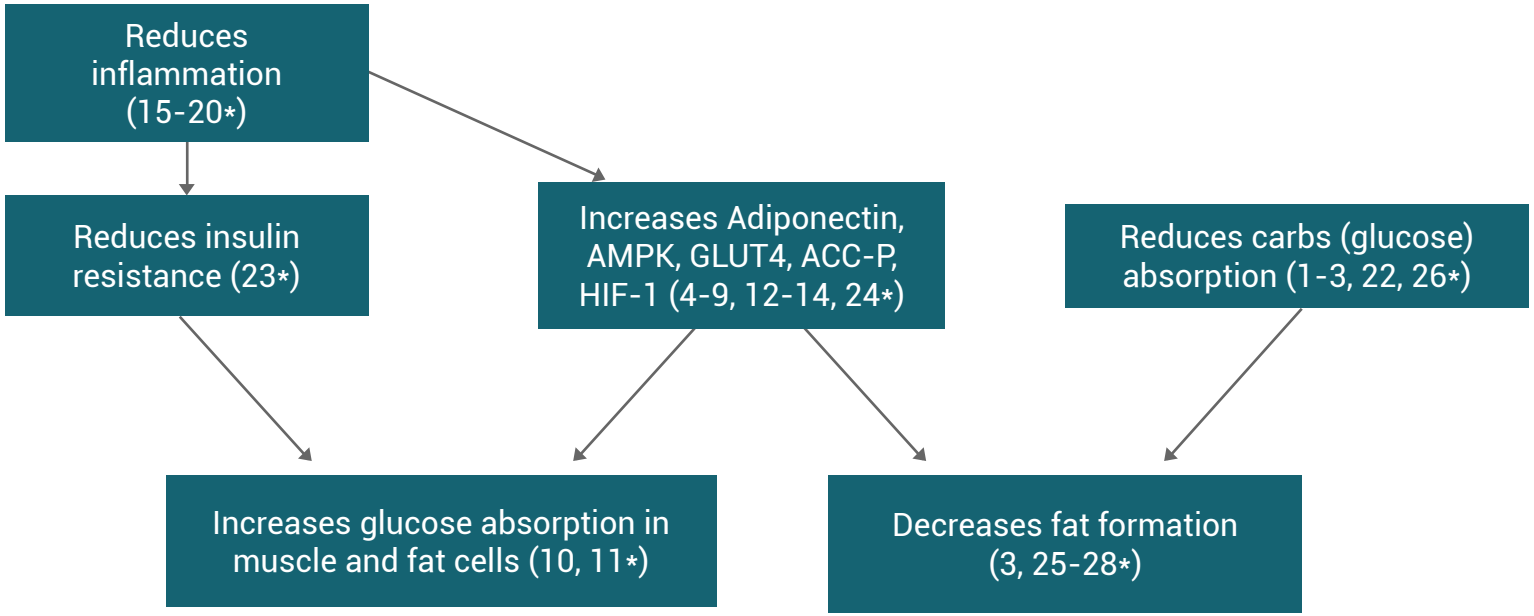
InnoSlim® reduces fat accumulation by inhibiting ACC activation (ACC-P) mediated by Adiponectin-AMPK pathway (5, 8, 10).

Adipose tissue contributes to local and systemic inflammation and disturbances in glucose homeostasis. InnoSlim® reduces inflammatory biomarkers PAI-1, RBP4 and TNFα in fat cells that are associated with insulin resistance and metabolic syndrome (5, 11, 12).

All the above effects suggest InnoSlim® may initiate a shift in energy homeostasis in favor of fatty acid breakdown to correct the glucose and fatty acid metabolic derailment that leads to weight gain and other metabolic dysfunctions.

For more details, please view the scientific papers

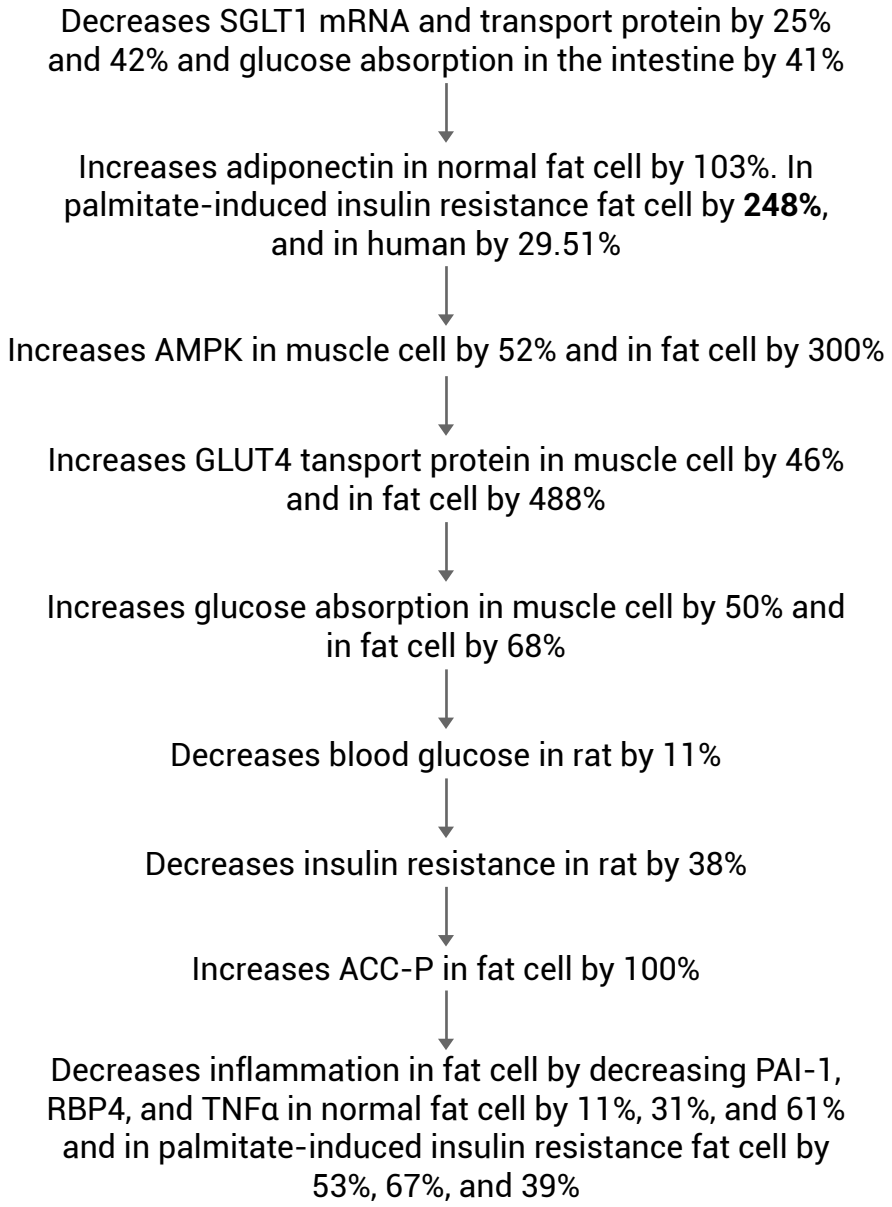
HOW INNOSLIM® WORKS



*Numbers 1-28 refer to the horizontal bars on slide 10

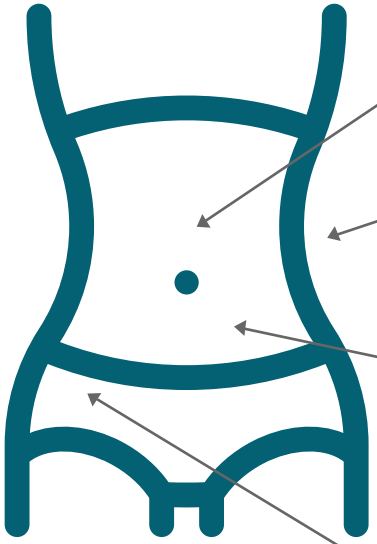
Adiponectin activity level affects AMPK, which in turn affects GLUT4, ACC-P, and HIF-1 activity levels. Increasing adiponectin activity increases the activities of AMPK, GLUT4, ACC-P, and HIF-1. ACC-P, GLUT4 and HIF-1 regulate fat acid oxidation, blood glucose levels (glucose absorption in muscle and fat cells), and glucose burning (conversion of glucose to energy (ATP)).

HOW INNOSLIM® WORKS



Reference: 1, 2, 3, 5, 8, 10, 11, 12

HOW INNOSLIM® WORKS



Reduces glucose absorption in the intestine by 42% by down regulating the SGLT1 transporter

Increases glucose absorption in muscle and fat cells by 50% and 68% by up regulating GLUT4 transporter

Decreases fatty acid formation by up regulating ACC-P

Reduces inflammation in fat cell to increase adiponectin in blood plasma and to reduce insulin resistance by down regulating inflammatory cytokines PAI-1, RPB4, and TNFα

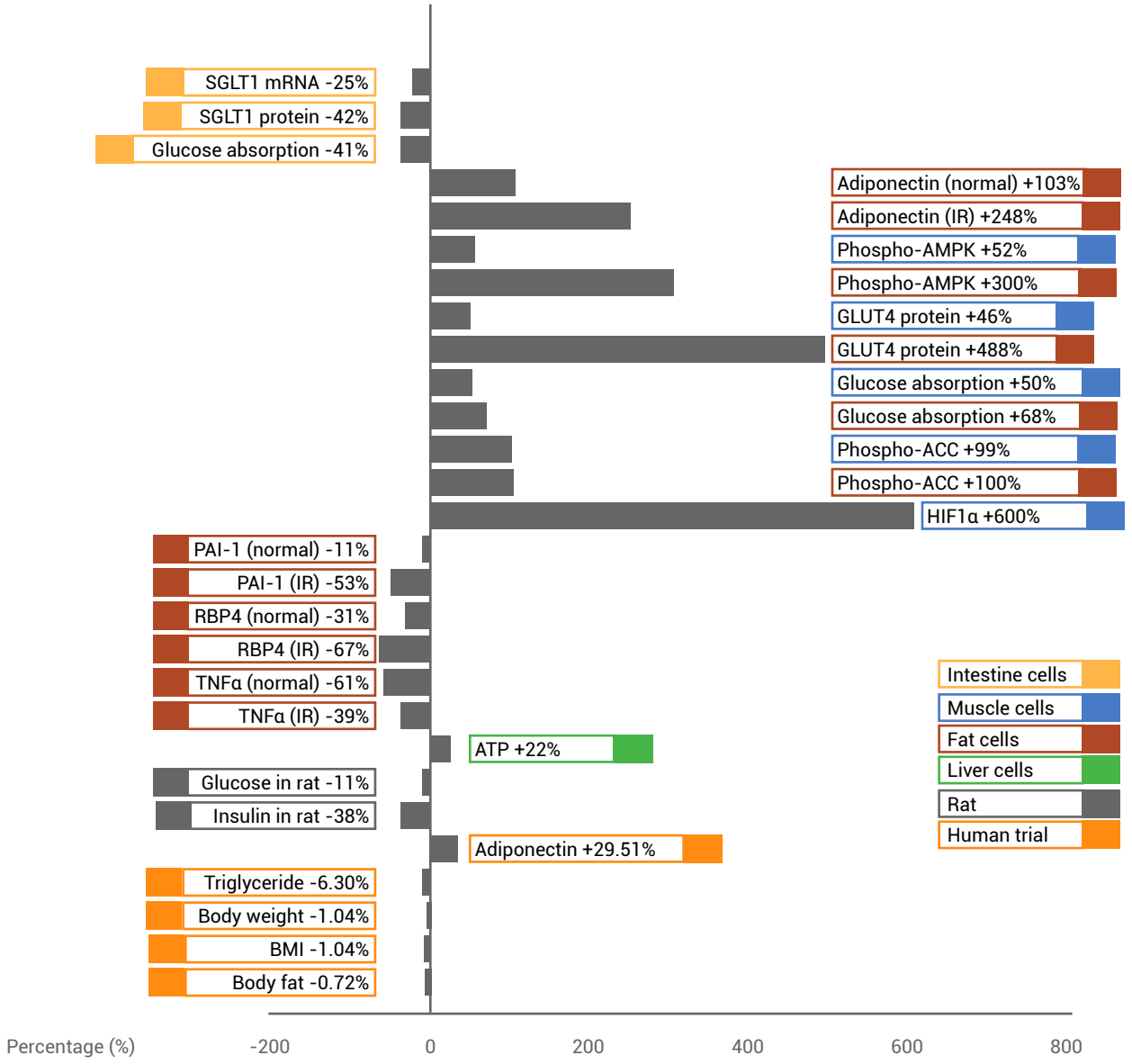
Reduces blood glucose in rat by 11%; reduces triglycerides in human by 6.3%; reduces body fat in human by **0.72%**; decreases insulin resistance in rat by 38%

Changes in weight, triglyceride, glucose and insulin level, satiety

Adiponectin activity level affects AMPK, which in turn affects GLUT4, ACC-P, and HIF-1 activity levels. Increasing adiponectin activity increases the activities of AMPK, GLUT4, ACC-P, and HIF-1. ACC-P, GLUT4 and HIF-1 regulate fat acid oxidation, blood glucose levels (glucose absorption in muscle and fat cells), and glucose burning (conversion of glucose to energy (ATP)).

Reference: 1, 2, 3, 5, 8, 10, 11, 12

KEY FINDINGS



Reference: 5

SUMMARY OF PRE-CLINICAL AND CLINICAL STUDIES

Improves glucose and fat metabolism:

- Decrease glucose absorption in the intestine
- Increase glucose absorption in muscle and fat cells
- Decrease glucose in circulation
- Less fat accumulation
- Less insulin resistance
- Less inflammation
- Less hunger

In-vitro

- Decreases glucose absorption in the intestine through down regulated SGLT1, mRNA and transport protein
- Increases adiponectin → Increases AMPK → Increases GLUT4 → Increases glucose absorption in muscle and fat cells
- Decreases inflammation in fat cell by down regulating PAI-1, RBP4, TNFα in normal fat cell and palmitate-induced insulin resistance fat cell

Reference: 1, 2, 3, 5, 8, 10, 11, 12

SUMMARY OF PRE-CLINICAL AND CLINICAL STUDIES

Validate the normal glucose and fat metabolic pathway is activated per the 18 *in-vitro* studies and result in the decrease of glucose and increase of insulin sensitivity.

In-vivo

Decreased blood glucose by 11% → Increases insulin sensitivity by 38%

Reference: 1, 2, 3, 5, 8, 10, 11, 12

SUMMARY OF PRE-CLINICAL AND CLINICAL STUDIES

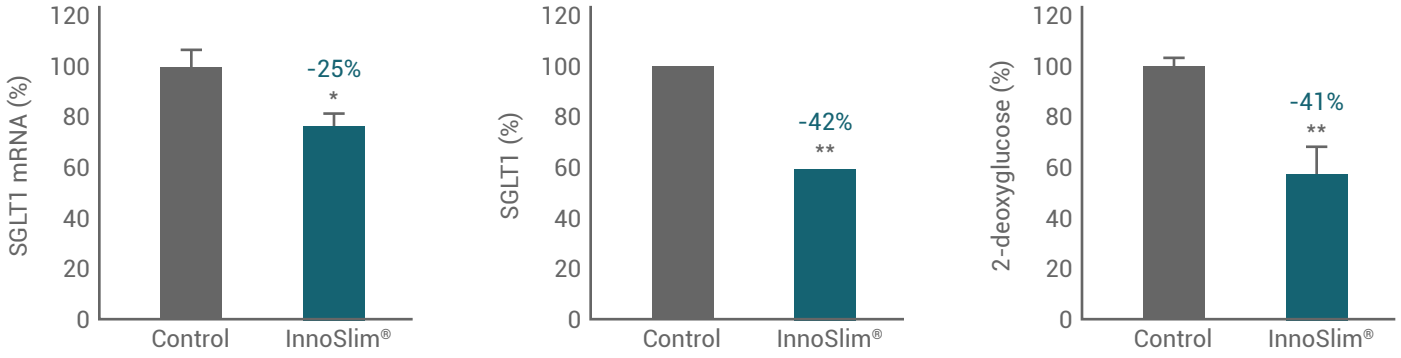
Validate the normal glucose and fat metabolic pathway is activated in humans as well.

Human clinical (an unrestricted calorie diet study)

Increases adiponectin by 3.26 µg/ml (29.51%) → Decreases triglyceride by 6.48mg/dl (6.30%) → Increases GLUT4 → Increases glucose absorption in muscle and fat cells

Reference: 1, 2, 3, 5, 8, 10, 11, 12

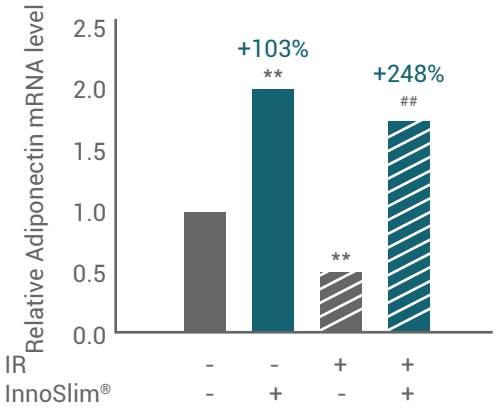
INNOSLIM® DECREASES GLUCOSE ABSORPTION IN THE INTESTINE (IN-VITRO)



*p < 0.05, when compared to the control group
**p < 0.01, when compared to the control group

Decreased SGLT1 mRNA leads to decreased SGLT1 transport protein to decreased glucose absorption in intestinal cell (Caco-2 cell)

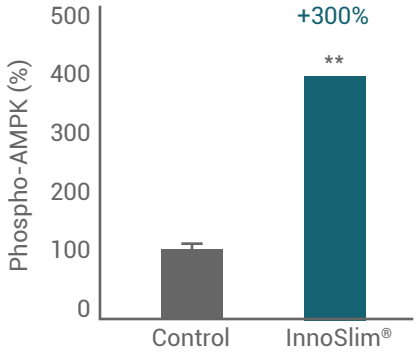
INNOSLIM® INCREASES ADIPONECTIN mRNA IN FAT (3T3-L1) CELL



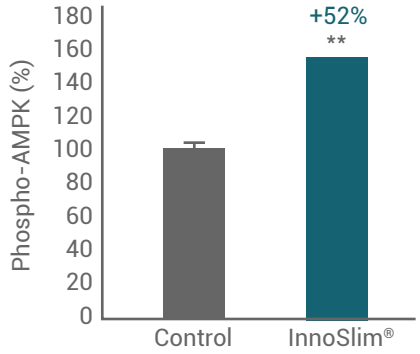
**p < 0.01, when compared to the control group
##p < 0.01, when compared to the IR group

Adiponectin is a protein hormone that regulates glucose levels and fatty acid oxidation. Increased adiponectin decreases fat cell formation and increases energy expenditure. Adiponectin plays a role in the suppression of obesity, type 2 diabetes, and atherosclerosis. InnoSlim® has shown to increase the adiponectin in normal fat cell by 103% and in palmitate-induced insulin resistance (IR) fat cell by 248%.

INNOSLIM® INCREASES AMPK PHOSPHORYLATION IN FAT (3T3-L1) AND MUSCLE (HSMMT) CELLS



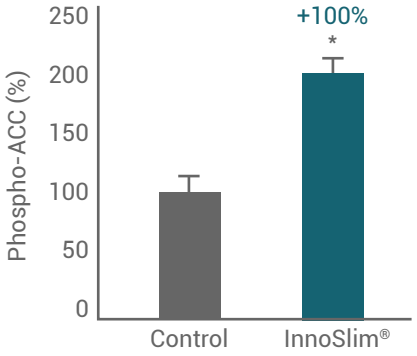
Fat cells
**p < 0.01, when compared to the control group



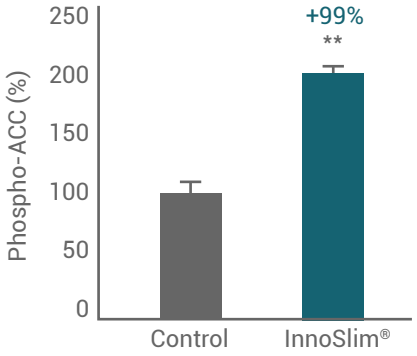
Muscle cells
**p < 0.01, when compared to the control group

Adenosine monophosphate-activated protein kinase (AMPK) is an enzyme that plays a role in cellular energy homeostasis. AMPK activation stimulates hepatic fatty acid oxidation, ketogenesis, skeletal muscle fatty acid oxidation and glucose uptake, inhibits cholesterol and triglyceride synthesis, lipogenesis, and modulation of insulin secretion by pancreatic beta-cells. InnoSlim® has shown to increase AMPK in fat cell by 300% and in muscle cell by 52%.

INNOSLIM® INCREASES ACC PHOSPHORYLATION IN FAT (3T3-L1) AND MUSCLE (HSMMT) CELLS



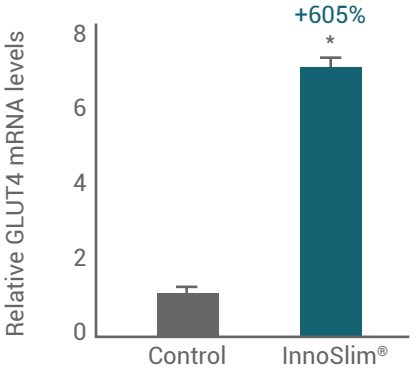
Fat cells
*p < 0.05, when compared to the control group



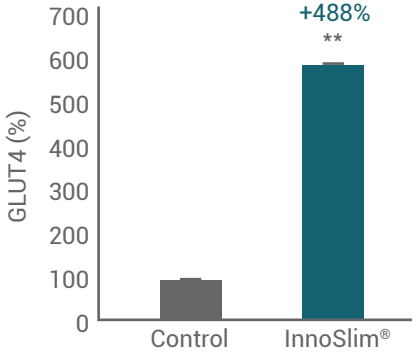
Muscle cells
**p < 0.01, when compared to the control group

Acetyl Coenzyme A carboxylase (ACC) is an enzyme that regulates the metabolism of fatty acids. Inhibition of ACC activity (increases phosphorylation of ACC (ACC-P)) reduces fatty acids formation. InnoSlim® has shown to increase ACC-P in fat cell by 100% and in muscle cell by 99%.

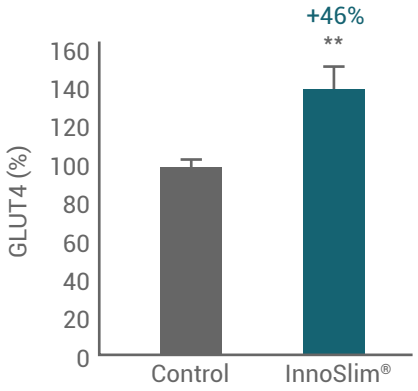
INNOSLIM® INCREASES GLUT4 TRANSPORT PROTEIN AND FAT (3T3-L1) AND MUSCLE (HSMMT) CELLS



Fat cells mRNA
**p < 0.01, when compared to the control group



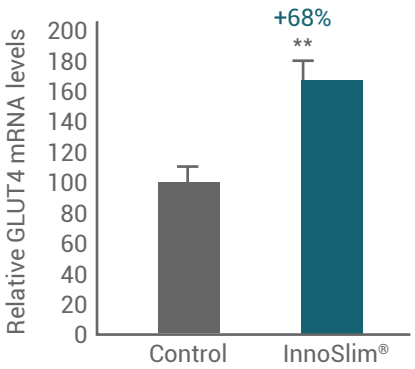
Fat cells transport protein
**p < 0.01, when compared to the control group



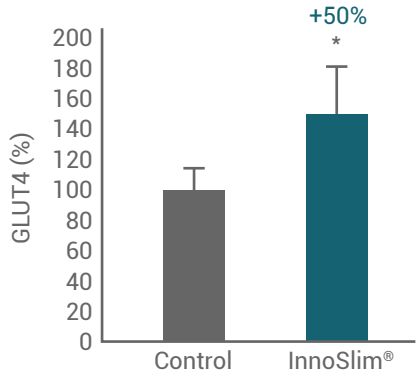
Muscle cells transport protein
**p < 0.01, when compared to the control group

Glucose transporter type 4 (GLUT4) is a insulin-regulated glucose transport protein found primarily in adipose tissues and skeletal and cardiac muscles. Increased GLUT4 level increases the absorption of glucose in muscles and decreases circulating glucose in blood stream. InnoSlim® has shown to increase GLUT4 mRNA and transport protein in fat cell by 605% and 488% respectively. InnoSlim® has also shown to increase GLUT4 transport protein in muscle cell by 46%.

INNOSLIM® INCREASES GLUCOSE ABSORPTION IN FAT (3T3-L1) CELLS AND MUSCLE (HSMMT) CELLS



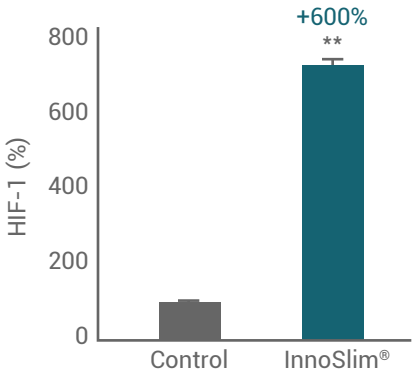
Fat cells
**p < 0.01, when compared to the control group



Muscle cells
*p < 0.05, when compared to the control group

InnoSlim® has shown to increase absorption of glucose in fat cell by 68% and in muscle cell by 50% as the result of increased GLUT4 mRNA and transport protein in fat and muscle cells.

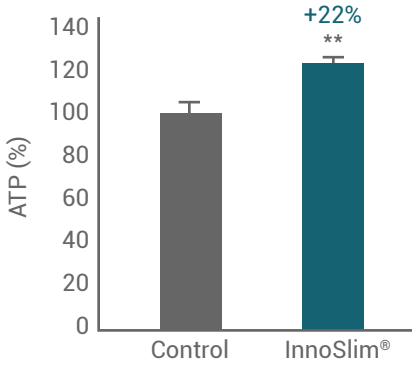
INNOSLIM® INCREASES HIF-1 IN MUSCLE (HSMMT) CELLS



HIF1
**p < 0.01, when compared to the control group

Hypoxia-inducible factor 1 (HIF-1), a transcription factor, is critical for systemic homeostasis to micro-environmental stimuli, e.g. hypoxia and low energy. Activation of HIF-1 has a positive effect on glycolysis process, oxygen and energy homeostasis. InnoSlim® has shown to increase HIF-1 in muscle cell by 600%.

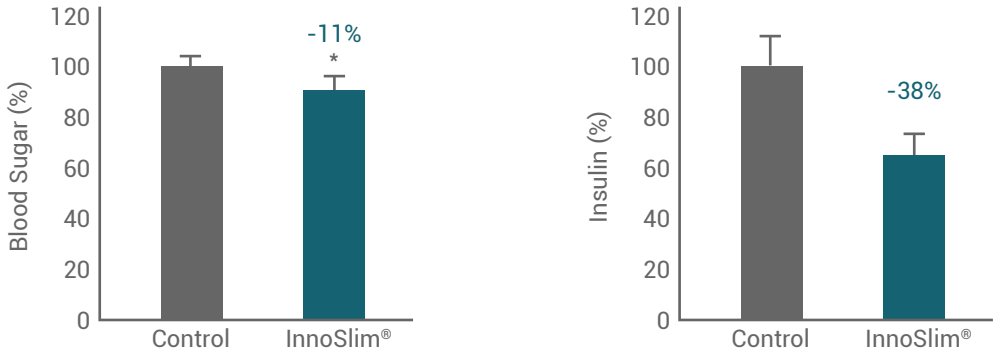
INNOSLIM® INCREASES ATP IN LIVER (HEPG2) CELL



ATP
**p < 0.01, when compared to the control group

Adenosine Triphosphate (ATP) is the primary energy carrier in all living organisms on earth. Microorganisms capture and store energy metabolized from food and light sources in the form of ATP. When the cell requires energy, ATP is broken down through hydrolysis. The high energy bond is broken and a phosphoryl group is removed. The energy released from this process is used to drive various cellular processes. ATP is constantly formed and broken down as it participates in biological reactions and it is central to the health and growth of all life. Without it, cells could not transfer energy from one location to another, making it impossible for organisms to grow and reproduce. InnoSlim® has shown to increase ATP production in liver cell by 22%.

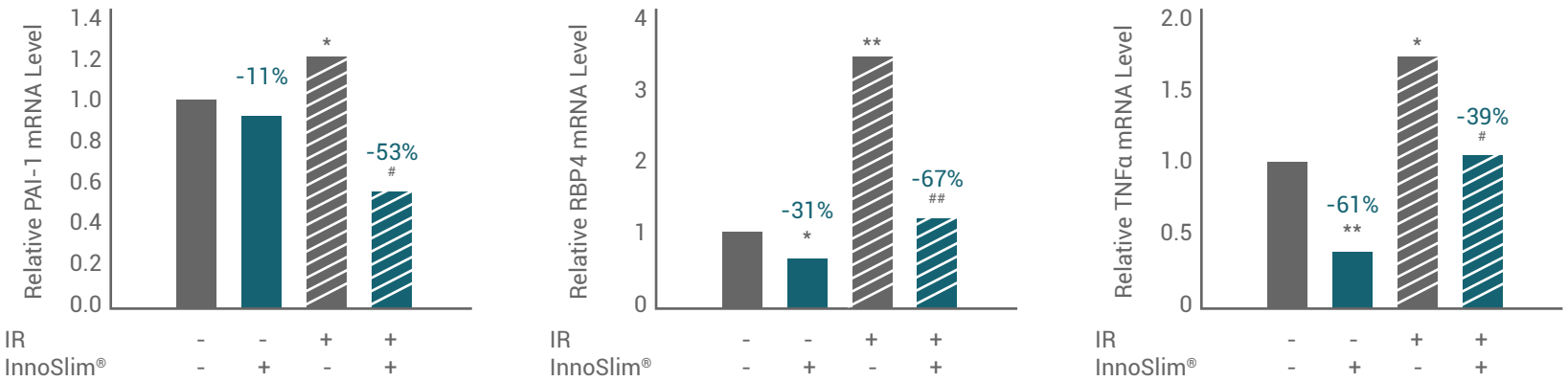
INNOSLIM® DECREASES GLUCOSE AND INSULIN IN RAT (IN-VIVO)



**p < 0.05, when compared to the control group

Glucose level in blood is tightly regulated in a narrow range. When glucose constantly goes beyond the upper limit, insulin resistance developed and eventually lead to many metabolic syndrome, including obesity, diabetes, and atherosclerosis. InnoSlim® has shown to reduce blood glucose and insulin in rats by 11% and 38%.

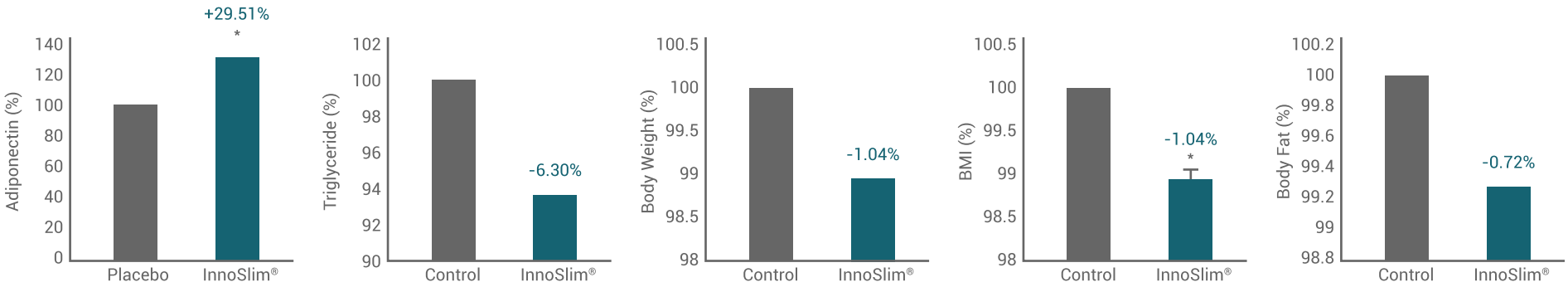
INNOSLIM® DECREASES INFLAMMATORY CYTOKINES mRNA IN NORMAL AND PALMITATE-INDUCED INSULIN RESISTANCE (IR) FAT (3T3-L1) CELL



*p < 0.05, when compared to the control group
**p < 0.01, when compared to the control group
#p < 0.05, when compared to the IR group
##p < 0.01, when compared to the IR group

Plasminogen Activator Inhibitor-1 (PAI-1) is significantly induced in insulin resistant, diabetes and metabolic syndrome; Retinol binding protein 4 (RBP4), expressed and secreted by adipose tissue, is strongly associated with insulin resistance; and Tumor necrosis factor-α (TNFα) in fat cells. As adipose tissue expands during obesity, there is an increase in inflammatory cytokines and a reduction in anti-inflammatory cytokines such as adponectinv, which contributes to local and systemic inflammation and disturbances in glucose homeostasis. InnoSlim® has shown to reduce PAI-1 in normal fat cell by 11% and in palmitate-induced insulin resistance (IR) fat cell by 53%. InnoSlim® has also shown to reduce RBP4 level in normal fat cell by 31% and in palmitate-induced IR fat cell by 67%. Finally, InnoSlim® has shown to reduce TNFα level in normal fat cell by 61% and palmitate-induced IR fat cell by 39%.

INNOSLIM®'S EFFECT FROM AN UNRESTRICTED CALORIE DIET RANDOMIZED DOUBLE-BLIND, PLACEBO-CONTROLLED CROSS OVER HUMAN STUDY



*p < 0.05, when compared to the placebo group

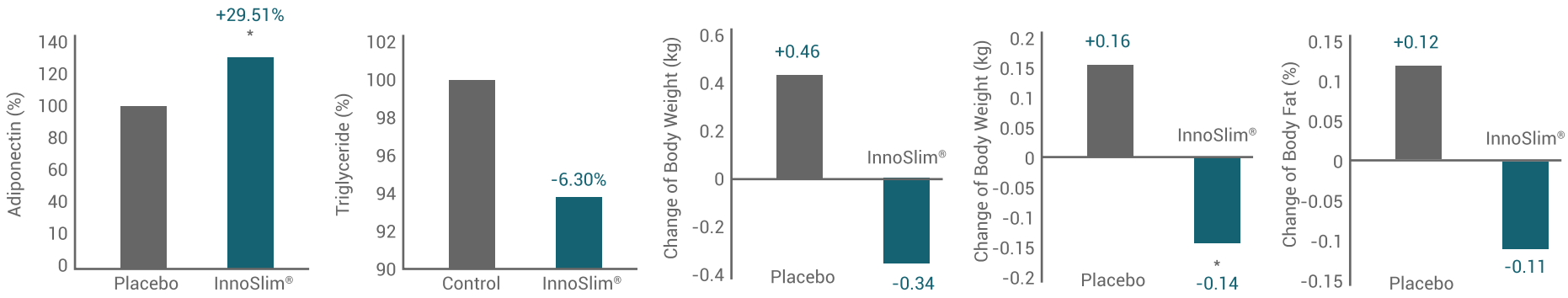
InnoSlim® has shown in this human study to induce statistically significant change in adiponectin (+29.51%) and BMI (-1.04%); change in triglyceride (-6.30%), body weight (-1.04%) and body fat (-0.72%) in the tested subjects.

These results are consistent with the 18 *in-vitro* and 2 *in-vivo* studies completed prior to the study, i.e., InnoSlim®.

1. Reduces glucose in blood plasma to reduce triglyceride that leads to fat accumulation and insulin resistance through the decreased glucose absorption in the intestine and increased glucose absorption in muscle and fat cells; (1,2,3,5)
2. Decreases inflammation in fat cell to reduce insulin resistance and to increase Adiponectin in blood plasma (10,11,12)
3. Increases adiponectin that leads to the activation of AMPK, GLUT4, ACC-P, and HIF-1 to decrease fat cell formation and to increase energy expenditure; (4,5,8,10)

The effects of InnoSlim® on the glucose and fat metabolic pathways cause, in our assessment, a fundamental shift in energy homeostasis in favor of less fat accumulation and more fatty acids breakdown to correct the underlying glucose and fatty acid metabolic derailment that lead to weight and other metabolic dysfunctions.

INNOSLIM®'S EFFECT FROM AN UNRESTRICTED CALORIE DIET RANDOMIZED DOUBLE-BLIND, PLACEBO-CONTROLLED CROSS OVER HUMAN STUDY



*p < 0.05, when compared to the placebo group

InnoSlim® has shown in this human study to induce statistically significant change in adiponectin (+29.51%) and BMI (-0.3kg/m2); change in triglyceride (-6.30%), body weight (-0.8kg) and body fat (-0.23%)) in the tested subjects.

These results are consistent with the 18 *in-vitro* and 2 *in-vivo* studies completed prior to the study, i.e., InnoSlim®.

1. Reduces glucose in blood plasma to reduce triglyceride that leads to fat accumulation and insulin resistance through the decreased glucose absorption in the intestine and increased glucose absorption in muscle and fat cells; (1,2,3,5)
2. Decreases inflammation in fat cell to reduce insulin resistance and to increase adiponectin in blood plasma (10,11,12)
3. Increases adiponectin that leads to the activation of AMPK, GLUT4, ACC-P, and HIF-1 to decrease fat cell formation and to increase energy expenditure; (4,5,8,10)

The effects of InnoSlim® on the glucose and fat metabolic pathways cause, in our assessment, a fundamental shift in energy homeostasis in favor of less fat accumulation and more fatty acids breakdown to correct the underlying glucose and fatty acid metabolic derailment that lead to weight and other metabolic dysfunctions.

REFERENCES

1. T.C. Chang, etc. Effect of Ginsenosides on Glucose Uptake in Human Caco-2 Cells Is Mediated through Altered Na+/Glucose Cotransporter 1 Expression. *J. Agric. Food Chem.* 2007, 55, 1993-1998.

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