

# VasoDrive-AP<sup>®</sup> Clinical Evidence

## The Journal of Clinical Hypertension

Germino FW, Neutel J, Nonaka M, Hendler SS. The impact of lactotripeptides on blood pressure response in stage 1 and stage 2 hypertensives. *J Clin Hypertens (Greenwich)*. 2010;12(3):153-9..

Topic	What effect does VasoDrive-AP <sup>®</sup> have on Stage 1 and 2, ambulatory-monitored hypertensive patients?
<b>Background</b>	<p>Nearly 70 million Americans have hypertension, and an estimated 70 million more have prehypertension, a condition carrying additional cardiovascular risk and sustained hypertension. For every 20- and 10-mm Hg increase in blood pressure (BP) greater than 115 and 75 mm Hg, respectively, there is a doubling of both cardiovascular and cerebrovascular risk.</p> <p>A prospective, randomized, double-blind endpoint parallel group study was conducted with newly diagnosed patients never treated before or patients who were uncontrolled on previous antihypertensive medication. The latter were slowly taken off antihypertensive medication and observed for a 3- to 4-week period before the study. Following at least 3 weeks of placebo run-in therapy, patients were randomized in a 2:1 ratio to either VasoDrive-AP<sup>®</sup> 75 mg BID or matching placebo. Patients remained in the double-blind treatment phase of the study for a total of 6 weeks. All study medication was dispensed in powder form in sealed sachets and then dissolved in apple juice (supplied for standardization). If mean systolic BP at any clinic visit exceeded 179 mm Hg and/or diastolic BP exceeded 109 mm Hg, patients were discontinued from the study and treated.</p>
<b>Study Type</b>	Human intervention study
<b>Study Design</b>	Prospective, randomized, double-blind endpoint parallel group study (24-hour ambulatory monitoring)
<b>Subjects</b>	91 previously treated and treatment-naive patients with Stage 1 and Stage 2 hypertension enrolled, with 10 dropping out
<b>Dosage</b>	VasoDrive-AP <sup>®</sup> 75 mg twice daily
<b>Results</b>	In this population, daytime systolic BP, the primary efficacy endpoint, significantly decreased (3.6 mm Hg; $p = .013$ ), while placebo did not affect systolic BP (0 mm Hg; $p$ not significant). Treatment-naive patients exhibited a more robust drop in their daytime systolic BP (-7.6 mm Hg; $p = .005$ ) compared with placebo (-3.6 mm Hg; $p =$ not significant). Lactotripeptides may be an effective agent in the management of low-risk and low-grade hypertension and prehypertension.
<b>Conclusion</b>	The reductions demonstrated in a large population could have a profound impact on cardiovascular and cerebrovascular risk. The reduction of BP was most significant in treatment-naive patients reluctant to begin drug therapy. It is estimated that even a 5-mm Hg reduction in systolic BP results in a 14% reduction in stroke mortality, a 9% reduction in coronary artery disease, and a 7% decline in total mortality.

## Clinical and Experimental Hypertension

Yamasue K, Morikawa N, Mizushima S, Tochikubo O. The blood pressure lowering effect of lactotripeptides and salt intake in 24-h ambulatory blood pressure measurements. *Clin Exp Hypertens*. 2010;32(4):214-20.

Topic	How does level of salt intake affect the antihypertensive effect of lactotripeptides?
<b>Background</b>	Sour milk containing lactotripeptides has a blood pressure-lowering effect. This study evaluated the blood pressure (BP)-lowering effect of lactotripeptides by monitoring home blood pressure, 24-hour ambulatory measurements (ABPM), and daily urinary salt excretion. A total of 30 volunteers were given 200 mL of sour milk twice a day for 8 weeks after a 1-week run-in period. This preparation contained the lactotripeptides valine-proline-proline (2.66 mg) and isoleucine-proline-proline (1.38 mg). The study participants had daily measurements of urinary salt excretion determined by an electric salt sensor and home blood pressure monitoring for each week during the run-in period, before the 4- and 8-week time points. Twenty-four-hour ABPM was measured at the end of each week.
<b>Study Type</b>	Human intervention trial
<b>Study Design</b>	Open-label human clinical trial
<b>Subjects</b>	30 volunteers
<b>Dosage</b>	200 mL of sour milk twice a day containing the lactotripeptides valine-proline-proline (2.66 mg) and isoleucine-proline-proline (1.38 mg)
<b>Results</b>	Mean systolic blood pressure (SBP) during night sleep including base BP at 4 and 8 weeks was significantly lower than base line values with the lactotripeptide treatment. Mean SBP and diastolic blood pressure (DBP) were significantly decreased at 4 and 8 weeks during sleep in the 22 participants who were categorized according to criteria of hypertension by 24-hour ABPM. The change in 24-hour mean SBP significantly correlated with mean urinary salt excretion over the three measurement periods. The 22 hypertensive subjects not taking lactotripeptides did not show significant change of blood pressure during 24 hours at 4 and 8 weeks.
<b>Conclusion</b>	The study confirmed the blood pressure-lowering effect of lactotripeptides during nighttime sleep and found a synergism in which a lower intake of salt increases the BP-lowering effect of lactotripeptides over a 24-hour period in hypertensive subjects.

# VasoDrive-AP<sup>®</sup> Clinical Evidence

## Atherosclerosis

Nakamura T, Mizutani J, Ohki K, et al. Casein hydrolysate containing Val-Pro-Pro and Ile-Pro-Pro improves central blood pressure and arterial stiffness in hypertensive subjects: a randomized, double-blind, placebo-controlled trial. *Atherosclerosis*. 2011;219(1):298-303.

<b>Topic</b>	What are the effects of casein hydrolysate containing milk-derived tripeptides val-pro-pro (VPP) and ile-pro-pro (IPP) on central blood pressure and arterial stiffness?
<b>Background</b>	Casein hydrolysate containing VPP and IPP milk protein tripeptides improves central systolic blood pressure (SBP) and brachial-ankle pulse wave velocity (baPWV), a measure of arterial health and unimpeded blood flow in hypertensive subjects, which suggests VPP and IPP might have beneficial effects on arterial properties. A randomized, double-blind, placebo-controlled trial was conducted in 70 Japanese subjects ages 50–69 with untreated Stage 1 hypertension who were randomly assigned to two groups, placebo tablets or active tablets containing 3.4 mg of VPP and IPP. At the beginning and end of the 8-week clinical study, hemodynamic parameters, including central SBP and baPWV, were measured.
<b>Study Type</b>	Human intervention trial
<b>Study Design</b>	Randomized, double-blind, placebo-controlled
<b>Subjects</b>	70 Japanese subjects ages 50–69 with untreated Stage 1 hypertension
<b>Dosage</b>	3.4 mg of val-pro-pro (VPP) and ile-pro-pro (IPP) daily
<b>Results</b>	A significant difference in the change of central SBP between the groups was observed, with a decrease of $11.0 \pm 11.0$ versus placebo ( $4.5 \pm 9.6$ mm Hg, $p < 0.01$ ). The active group showed reductions in baPWV of $73.9 \pm 130.0$ versus $8.4 \pm 137.1$ cm/s ( $p < 0.05$ ) and brachial SBP decreases of $10.5 \pm 11.5$ versus $3.9 \pm 9.6$ mm Hg ( $p < 0.05$ ). Radial mean blood pressure decreases of $7.3 \pm 8.9$ were significantly greater than decreases of $2.0 \pm 7.4$ mm Hg ( $p < 0.01$ ) in the placebo group.
<b>Conclusion</b>	For the first time, an 8-week intervention with milk-derived tripeptides VPP and IPP significantly improved both central systolic blood pressure and arterial stiffness compared with placebo in untreated Stage 1 hypertensive subjects. These results suggest that intake of foods containing VPP and IPP might have beneficial effects on arterial properties and cardiovascular event risk prevention in those in the early stage of high blood pressure.

## Bioscience, Biotechnology, and Biochemistry

Ishida Y, Shibata Y, Fukuhara I, Yano Y, Takehara I, Kaneko K. Effect of an excess intake of casein hydrolysate containing Val-Pro-Pro and Ile-Pro-Pro in subjects with normal blood pressure, high-normal blood pressure, or mild hypertension. *Biosci Biotechnol Biochem*. 2011;75(3):427-33.

<b>Topic</b>	What is the effect of an excess dosage for evaluating safety of a casein hydrolysate product containing val-pro-pro and ile-pro-pro in subjects with normal blood pressure or mild hypertension?
<b>Background</b>	Milk fermented with <i>Lactobacillus helveticus</i> , a lactic acid bacterium with potent proteolytic activity, had antihypertensive effects in animal and human studies; however, other probiotics used to ferment milk do not show this effect. Two angiotensin I-converting enzyme (ACE) inhibitory tripeptides VPP and IPP have been identified from isolates of <i>L. helveticus</i> -fermented milk, and it is thought that the antihypertensive effect is due mainly to these two tripeptides, according to both an in vitro study and an animal model study. Another source of VPP and IPP is casein using a protease from <i>Aspergillus oryzae</i> to hydrolyze it.  A tablet containing casein hydrolysate was developed to be given at 5 times the normal level to observe its safety after 4 weeks of use. The study was a double-blind, placebo-controlled, randomized clinical trial of casein hydrolysate, incorporating ACE inhibitory peptides including VPP and IPP, in subjects with blood pressure ranging from normal to mildly hypertensive. A total of 48 subjects were given either 5 times more than the effective amount of casein hydrolysate or a placebo in tablet form for 4 weeks.
<b>Study Type</b>	Human intervention study
<b>Study Design</b>	Double-blind, placebo-controlled, randomized human clinical trial
<b>Subjects</b>	48 subjects with either normal blood pressure or mild hypertension
<b>Dosage</b>	One dose (20 tablets of 5.0 g/d) of the active tablet contained 7.5 mg of VPP and 9.6 mg of IPP; these tripeptides were not detected in the placebo tablet.
<b>Results</b>	In the active group, systolic blood pressure (SBP) decreased significantly compared with the placebo group. In stratified analysis, the antihypertensive effect was not found in subjects with normal blood pressure. Neither an acute or nor an excessive reduction in blood pressure nor clinically important adverse events were observed in the study.
<b>Conclusion</b>	The findings support the belief that intake of a fivefold excess of tablets containing casein hydrolysate can lead to a mild improvement in hypertension without side effects.

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## Journal of Medicinal Food

Kurosawa MT, Nakamura Y, Yamamoto N, Yamada K, Iketani T. Effects of Val-Pro-Pro and Ile-Pro-Pro on nondipper patients: a preliminary study. *J Med Food*. 2011;14(5):538-42.

<b>Topic</b>	What role do val-pro-pro and ile-pro-pro play in patients with Stage 1 hypertension and in nondipper patients (those who do not have low dips in blood pressure at different times)?
<b>Background</b>	Clinical evidence shows there are antihypertensive effects of the milk-derived antihypertensive peptides val-pro-pro and ile-pro-pro (lactotriptides). However, circadian rhythm effects determined by ambulatory blood pressure monitoring (ABPM) to eliminate the confounding influence of the white-coat effect have not been fully studied. Twelve hypertensive patients not receiving antihypertensive medication (2 men, 10 women; mean age $\pm$ standard deviation, 63.5 $\pm$ 8.3 years) who had been visiting a clinic for more than 1 year participated in a study. The mean ( $\pm$ standard deviation) systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 142.4 $\pm$ 2.6 and 83.5 $\pm$ 6.4 mm Hg, respectively.
<b>Study Type</b>	Human intervention study
<b>Study Design</b>	The study was a small, nonparallel trial performed open-label at a single clinical center.
<b>Subjects</b>	Twelve hypertensive patients not receiving antihypertensive medication (2 men, 10 women)
<b>Dosage</b>	Fermented milk product containing antihypertensive tripeptides val-pro-pro (2.53 mg) and 1.52 mg ile-pro-pro (1.52 mg)

<b>Results</b>	After patients had ingested a fermented milk product containing antihypertensive tripeptides val-pro-pro (2.53 mg) and ile-pro-pro (1.52 mg) for more than 4 weeks, both office SBP and DBP were significantly reduced to a mean ( $\pm$ standard deviation) of 133.3 $\pm$ 7.0 mm Hg and 76.5 $\pm$ 8.4 mm Hg ( $p < .001$ and $p < .005$ by paired t-test), respectively. The 24-hour SBP and DBP determined by ABPM were reduced from 127.3 $\pm$ 2.4 and 78.7 $\pm$ 2.3 mm Hg to 120.2 $\pm$ 2.4 and 75.0 $\pm$ 2.2 mm Hg ( $p < .001$ and $p < .05$ ), respectively. Awake-time SBP (08:00–21:00), nighttime SBP (0:00–05:00), and early-morning SBP (06:00–07:00) were reduced from 130.9 $\pm$ 2.4 to 123.3 $\pm$ 2.3 mm Hg, 118.7 $\pm$ 2.9 to 113.2 $\pm$ 3.4 mm Hg, and 132.8 $\pm$ 4.3 to 122.4 $\pm$ 3.9 mm Hg (by paired t-test: $p < .001$ , $p < .05$ , and $p < .05$ ), respectively. Of DBP measured by ABPM, 24-hour DBP and awake-time DBP were significantly reduced from 78.7 $\pm$ 2.3 to 75.0 $\pm$ 2.2 mm Hg and 82.1 $\pm$ 2.5 to 77.3 $\pm$ 2.2 mm Hg ( $p < .05$ and $p < .01$ ), respectively. Clinic BP and 24-hour blood pressure did not significantly differ between the dipper and nondipper groups at base line. Nighttime and early morning blood pressure were significantly reduced after treatment from base line in the nondipper group (-8.5 $\pm$ 2.5 and -15.6 $\pm$ 3.7 mm Hg; $p < .05$ and $p < .01$ , respectively) but not in the dipper group (-2.5 $\pm$ 3.6 and -1.2 $\pm$ 4.7 mm Hg; $p$ not significant). Reduction in early morning blood pressure significantly differed between the groups ( $p < .05$ ).
<b>Conclusion</b>	The results suggest that the milk tripeptides decrease blood pressure in patients with Stage 1 hypertension and result not only in lower blood pressure at nighttime but also in lower early morning SBP in nondipper patients.

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*American Journal of Physiology: Heart and Circulatory Physiology*  
Yoshizawa M, Maeda S, Miyaki A, et al. Additive beneficial effects of lactotripeptides and aerobic exercise on arterial compliance in postmenopausal women. *Am J Physiol Heart Circ Physiol.* 2009;297(5):H1899-903.

<b>Topic</b>	<b>What is the beneficial effect of lactotripeptides on arterial compliance in postmenopausal women?</b>
<b>Background</b>	Two active tripeptides, valine-proline-proline and isoleucine-proline-proline isolated from sour milk referred to as lactotripeptides (LTP), function as an angiotensin-converting enzyme inhibitor. This study investigated whether LTP improves arterial compliance alone or in combination with regular aerobic exercise. A total of 55 postmenopausal women (50–65 years old) were randomly divided into four groups: placebo, LTP only, exercise and placebo (Ex + placebo), and exercise and LTP (Ex + LTP). LTP or placebo was administered orally for 8 weeks. The exercise groups completed an 8-week moderate aerobic exercise intervention. There were no differences in base line arterial compliance and most other important dependent variables between the groups.
<b>Study Type</b>	Human intervention trial
<b>Study Design</b>	Randomized, double-blind, placebo controlled
<b>Subjects</b>	A total of 55 postmenopausal women (50–65 years old)
<b>Dosage</b>	Subjects in LTP and Ex + LTP groups ingested 2.8 g of casein hydrolysate powder containing 2.4 mg of valine-proline-proline and 4.3 mg of isoleucine-proline-proline per day, and this daily dose was divided into 8 capsules. An equivalent dose of sodium caseinate, the starting material for casein hydrolysate, was used as a placebo.
<b>Results</b>	Carotid arterial compliance increased significantly in the lactotripeptides-only group LTP ( $0.93 \pm 0.07$ versus $0.99 \pm 0.08$ mm <sup>2</sup> /mm Hg x 10 <sup>(-1)</sup> ), Ex + placebo ( $0.92 \pm 0.04$ versus $1.00 \pm 0.05$ mm <sup>2</sup> /mm Hg x 10 <sup>(-1)</sup> ), and Ex + LTP groups ( $0.86 \pm 0.06$ versus $1.00 \pm$ or $-0.06$ mm <sup>2</sup> /mm Hg x 10 <sup>(-1)</sup> ). No significant changes were observed in the placebo control group ( $0.86 \pm 0.06$ versus $0.85 \pm$ or $-0.07$ mm <sup>2</sup> /mm Hg x 10 <sup>(-1)</sup> ). The magnitude of increases in carotid arterial compliance was significantly greater in the Ex + LTP group (19% ± 4%) than in all other groups. The improvements in arterial compliance with LTP were associated with the corresponding reductions in arterial blood pressure and plasma angiotensin II concentrations.
<b>Conclusion</b>	LTP ingestion improves carotid arterial compliance, and the combination of LTP ingestion and regular exercise is additive and synergistic in improving arterial compliance in postmenopausal women.

*American Journal of Hypertension*  
Yoshizawa M, Maeda S, Miyaki A, et al. Additive beneficial effects of lactotripeptides intake with regular exercise on endothelium-dependent dilatation in postmenopausal women. *Am J Hypertens.* 2010;23(4):368-72.

<b>Topic</b>	<b>What additive effects are there of lactotripeptides intake with regular exercise on endothelium-dependent dilatation in postmenopausal women?</b>
<b>Background</b>	Peripheral conduit artery endothelium-dependent dilatation decreases with aging, and endothelial dysfunction precedes the appearance of clinical cardiovascular disease symptoms that may be involved in the pathogenesis of a number of cardiovascular disorders. Flow-mediated dilatation (FMD) is an endothelium-dependent dilatory response to an actual physiological stimulus such as increases in blood flow and vascular shear stress and reveals the overall health and functional integrity of the vascular endothelium. Endothelium-dependent dilatation decreases with advancing age in both men and women. Although premenopausal women are protected against the deleterious effect of aging on endothelial function, menopause is associated with the onset and worsening of age-related endothelial dysfunction.  Lactotripeptides (LTPs) and regular exercise can improve endothelium-dependent dilatation. The combined use may be more effective than either treatment by itself. A randomized, placebo-controlled trial with four intervention arms was conducted. A total of 43 postmenopausal women (50–65 years old) were randomly divided into placebo, LTP, exercise and placebo (Ex + placebo), and exercise and LTP (Ex + LTP) groups. LTP or placebo was administered orally for 8 weeks. The exercise groups completed an 8-week moderate aerobic exercise (walking or cycling) intervention.
<b>Study Type</b>	Human intervention study
<b>Study Design</b>	Randomized, placebo-controlled trial
<b>Subjects</b>	43 healthy, sedentary postmenopausal women
<b>Dosage</b>	Subjects ingested 2.8 g of casein hydrolysate powder containing 2.4 mg of valine-proline-proline and 4.3 mg of isoleucine-proline-proline per day, divided into 8 capsules. An equivalent dose of sodium caseinate was used as a placebo.

<b>Results</b>	There were no significant differences in base line flow-mediated dilatation (FMD) and most other important dependent variables among the groups. FMD significantly increased in the LTP, Ex + placebo, and Ex + LTP groups, whereas no such changes were observed in the placebo control group. The size of increases in FMD was significantly greater in the Ex + LTP group than in other intervention groups.
<b>Conclusion</b>	It was concluded that LTP ingestion combined with regular aerobic exercise improves endothelium-dependent dilatation to a greater extent than monotherapy of each intervention alone in postmenopausal women.

## Hypertension Research

Hirota T, Ohki K, Kawagishi R, et al. Casein hydrolysate containing the antihypertensive tripeptides Val-Pro-Pro and Ile-Pro-Pro improves vascular endothelial function independent of blood pressure-lowering effects: contribution of the inhibitory action of angiotensin-converting enzyme. *Hypertens Res.* 2007;30(6):489-96.

<b>Topic</b>	<b>Do the antihypertensive tripeptides val-pro-pro and ile-pro-pro improve vascular endothelial function independent of blood pressure-lowering effects?</b>
<b>Background</b>	Accumulating evidence shows that deterioration of vascular endothelial function underlies the part of cardiovascular disease progression and etiology related to lifestyle-related diseases such as hypertension and dyslipidemia. Both val-pro-pro (VPP) and ile-pro-pro (IPP), which are tripeptides derived from proteolytic hydrolysate of milk casein, inhibit angiotensin-converting enzyme (ACE), suggesting that both VPP and IPP may improve vascular endothelial function. ACE inhibitors are known to improve endothelial function. This study investigated the effects of an ACE-inhibitory food component in people with mild hypertension. The study was conducted by the placebo-controlled, double-blind crossover method in 25 male subjects with mild hypertension. After casein hydrolysate containing both VPP and IPP was administered as a daily dose divided into 4 capsules for 1 week, reactive hyperemia of the left upper forearm was measured using plethysmography as an index of vascular endothelial function. One subject dropped out. The reactive hyperemia of the left upper forearm was created by a 5-minute occlusion using inflation of a cuff.
<b>Study Type</b>	Human intervention study
<b>Study Design</b>	Placebo-controlled, double-blind crossover design
<b>Subjects</b>	24 male subjects with mild hypertension
<b>Dosage</b>	Subjects ingested 1.25 g of casein hydrolysate powder containing 3.42 mg of VPP and 3.87 mg of IPP per day
<b>Results</b>	The maximum blood flow during reactive hyperemia was $20.8 \pm 6.7$ mL/min/100 mL tissue in the placebo group, whereas it increased to a surprising level of $30.0 \pm 10.4$ mL/min/100 mL tissue in the group administered casein hydrolysate containing both VPP and IPP ( $p < 0.001$ ). There was no change in systemic blood pressure, indicating that the improvement of the vascular endothelial function attributable to VPP and IPP is independent of hemodynamic changes.
<b>Conclusion</b>	It was judged that casein hydrolysate containing VPP and IPP improves vascular endothelial dysfunction in subjects with mild hypertension.

## Hypertension Research

Cicero AF, Rosticci M, Gerocarni B, et al. Lactotriptides effect on office and 24-h ambulatory blood pressure, blood pressure stress response, pulse wave velocity and cardiac output in patients with high-normal blood pressure or first-degree hypertension: a randomized double-blind clinical trial. *Hypertens Res.* 2011;34(9):1035-40.

<b>Topic</b>	What effect do lactotriptides have on 24-hour ambulatory blood pressure, blood pressure stress response, pulse wave velocity, and cardiac output in patients with high-normal blood pressure or first-degree hypertension?
<b>Background</b>	<p>Enzymatic treatment of casein hydrolysate has antihypertensive effects from its lactotriptides (LTPs). Our aim was to evaluate this effect on a large number of hemodynamic parameters. A prospective double-blind, randomized clinical trial was conducted that included 52 patients affected by high-normal blood pressure (BP) or first-degree hypertension. The study was a 6-week treatment with the LTPs isoleucine-proline-proline and valine-proline-proline at 3 mg per day and involved office BP measurement, 24-h ambulatory BP monitoring (ABPM), stress-induced BP increase, and cardiac output-related parameters.</p> <p>The peptides are part of the primary structure of milk proteins and can be released by enzymatic hydrolysis, during either gastrointestinal digestion or food processing, and are thought to exert some angiotensin-converting enzyme inhibitory activity. The best-characterized peptides are those found in fermented milk that contains the amino acid tripeptide sequence isoleucine-proline-proline (IPP) and valine-proline-proline (VPP). In Japanese subjects only, investigations confirmed an effect of LTP on flow-mediated dilation, artery compliance, and central BP, and the antihypertensive effect of LTPs seem to be strongly related to the ethnicity of patients, so it would be beneficial to study the effect in European subjects. This study evaluated the effect of LTPs supplemented as functional food on a large number of hemodynamic parameters in southern European subjects with high-normal BP or first-degree hypertension.</p>
<b>Study Type</b>	Human intervention trial
<b>Study Design</b>	Randomized, double-blind clinical trial
<b>Subjects</b>	52 southern European subjects with high-normal BP or first-degree hypertension
<b>Dosage</b>	3 mg of lactotriptides (isoleucine-proline-proline and valine-proline-proline )

<b>Results</b>	In the LTP-treated subjects, a significant reduction was observed in the clinical setting of systolic blood pressure (SBP) ( $-5 \pm 8$ mm Hg, $p = 0.013$ ) and a significant improvement in pulse wave velocity (PWV) ( $-0.66 \pm 0.81$ m/s-1 $p = 0.001$ ), a biomarker of vascular rigidity. No effect was seen on 24-hour ABPM parameters and BP reaction to stress from treatment with the combined LTPs. LTPs, but not placebo, were associated with a mild but significant change in the stroke volume (SV), SV index (markers of cardiac flow), the acceleration index (ACI) and velocity index (VI) (markers of cardiac contractility). No effect was observed on parameters related to fluid dynamics or vascular resistance. LTPs positively influenced the clinical environment measurement of these vascular dynamic parameters.
<b>Conclusion</b>	VPP and IPP lactotriptides positively influenced office SBP, PWV, SV, stroke index, ACI, and VI in southern European patients with high-normal BP or first-degree hypertension.

**Nutrition Journal**

Iwasa M, Aoi W, Mune K, et al. Fermented milk improves glucose metabolism in exercise-induced muscle damage in young healthy men. *Nutr J.* 2013;12:83.

Topic	Does fermented milk improve glucose metabolism in exercise-induced muscle damage in healthy young men?
Background	<p>This study investigated the effect of fermented milk supplementation and the related casein-based peptides on glucose metabolism associated with muscle damage after acute exercise in humans.</p> <p>Strenuous exercise in those not used to it can cause muscle damage that results in muscular pain and involves protein degradation and ultrastructural changes, a condition known as delayed-onset muscle damage. The exercise-induced muscle damage is caused by several factors, including mechanical stress, calcium accumulation, and oxidative stress. It may be that muscle functions, such as energy metabolism and power output, cannot be maintained as well in damaged muscle. Glucose utilization as an energy substrate in the whole body is decreased in muscle damage after exercise due to an impairment of insulin-dependent glucose uptake in the damaged muscle and is related to oxidative stress and certain inflammatory cytokines via inactivation of insulin-signaling pathways in muscle cells. Infiltration of phagocytes into the damaged muscle is observed after strenuous exercise, and an inflammatory response is implicated in the development of delayed-onset muscle damage. It is thought by one of the principal theories of the physiological mechanism of action that the decrease of glucose metabolism associated with muscle damage may be prevented by the suppression of inflammation and oxidative stress. Some types of fermented milk also possess anti-inflammatory and antioxidant properties. <i>Lactobacillus helveticus</i>-fermented milk prevents muscle damage induced by acute exercise via activation of antioxidative enzymes of skeletal muscle in an animal study, which may support claims that fermented milk may prevent the impairment of glucose metabolism associated with muscle damage. This study investigated the effect of fermented milk supplementation on glucose metabolism in damaged muscle after acute resistance exercise in humans.</p> <p>Eighteen healthy young men participated in each of the three trials of the study, which included rest, exercise with placebo, and exercise with fermented milk supplementation. In the exercise trials, subjects carried out resistance exercise consisting of 5 sets of leg and bench presses at 70–100% 12-repetition maximum. Examination beverage (fermented milk or placebo) was taken before and after exercise in the double-blind method. The following day, we conducted an analysis of respiratory metabolic performance, blood collection, and evaluation of muscle soreness.</p>
Study Type	Human intervention study

Study Design	The subjects participated in 3 trials of the study: rest with placebo intake, exercise with placebo intake, and exercise with fermented milk intake in an experimental design with repeating parts. These trials were performed in a random order by a counterbalanced design and were separated by at least 6 weeks in any individual subject to avoid the biasing of muscle damage.
Subjects	Eighteen healthy young men who were not habituated to a regular exercise regimen were found to participate in the study. The characteristics of the subjects were as follows: age, 21.6 ± 0.8 years; height, 171.1 ± 1.5 cm; body weight, 59.9 ± 1.5 kg; body mass index, 20.5 ± 0.4 kg/m <sup>2</sup> ; and body fat, 16.2 ± 0.8%.
Dosage	<i>Lactobacillus helveticus</i> -fermented milk (Amiel S®, Calpis Co. Ltd., Tokyo, Japan) was used in the fermented milk trial. An equivalent dose of unfermented milk, with adjusted contents of protein (1.1%), fat (0%), carbohydrate (3.6%), and pH (3.75) to be similar to the fermented milk, was used as a placebo beverage. Subjects consumed 200 mL of each beverage 3 times before and after exercise by the double-blind method; therefore, their total energy intake was: 102 kcal, protein: 6.6 g, fat: 0.0 g, and carbohydrate: 21.6 g/600 mL.
Results	Muscle soreness was significantly suppressed by the consumption of fermented milk compared with placebo (placebo, 14.2 ± 1.2 score versus fermented milk, 12.6 ± 1.1, <i>p</i> < 0.05). Exercise significantly increased serum creatine phosphokinase, and this increase revealed a tendency of suppression after the consumption of fermented milk. Exercise significantly decreased the respiratory quotient (rest, 0.88 ± 0.01 versus placebo, 0.84 ± 0.02, <i>p</i> < 0.05); however, this decrease was counteracted by the consumption of fermented milk (0.88 ± 0.01, <i>p</i> < 0.05). The effect of exercise significantly reduced the absorption capacity of serum oxygen radicals (rest, 6.9 ± 0.4 μmol TE/g versus placebo, 6.0 ± 0.3 μmol TE/g, <i>p</i> < 0.05), although this reduction was not observed with the consumption of the test substance fermented milk (6.2 ± 0.3 μmol TE/g).
Conclusion	These results of this study support the idea that fermented milk supplementation improves glucose metabolism and reduces the effects of muscle soreness after high-intensity exercise, and is likely related to the regulation of antioxidant capacity.

# VasoDrive-AP<sup>®</sup> Clinical Evidence

## 12th Asian Congress of Nutrition

Miyazaki H, Nakamura T, Ohki K, et al. Milk casein hydrolysate lowered heart rate during downhill walking exercise and muscle damage after that in middle aged to elderly men, compared with those of placebo. Poster presented at: 12th Asian Congress of Nutrition; May 2015; Yokohama, Japan.

<b>Topic</b>	What effect does milk casein hydrolysate have in lowering heart rate during downhill walking exercise and reducing muscle damage afterward in middle-aged to elderly men, compared with placebo?
<b>Background</b>	<p>Val-Pro-Pro (VPP) and Ile-Pro-Pro (IPP) are milk tripeptides derived from milk casein that have effects on improving vascular endothelial dysfunction and vasodilatation, and fermented milk with <i>Lactobacillus helveticus</i> containing VPP and IPP have an alleviative effect on muscle damage after exercise. (Iwasa M et al., Nutr J. 2013). However, the effects of foods including these tripeptides on the vascular system during exercise, as well as the relationship between them and muscle damage after exercise, were still unknown. This study investigated the effects of milk casein hydrolysate (MCH) containing VPP and IPP on heart rate during exercise and on muscle damage in middle-aged to elderly men. Downhill walking exercise at a speed of 5 km/h and a -5 % grade over 30 minutes was implemented.</p> <p>The measurements included heart rate and blood parameters using a Holter monitor (RAC-2512, NIHON KOHDEN), which was used before and during exercise. Blood was collected before and after exercise to measure creatine kinase activity, insulin, and glucose level.</p> <p>Subjects ingested 4 tablets of the test substance 30 minutes before and 30 minutes after exercise.</p>
<b>Study Type</b>	Human intervention trial
<b>Study Design</b>	Randomized, double-blind, placebo-controlled crossover trial with a 2-week washout period
<b>Subjects</b>	14 healthy middle-aged to elderly men (53.1 ± 6.7 years old)
<b>Dosage</b>	8 casein hydrolysate tablets, which contains 6.8mg of VPP and IPP. 4 tablets 30 minutes before and 3 tablets 30 minutes after exercise.
<b>Results</b>	Heart rate was about 4 beats lower in MCH group versus control. Creatine kinase was significantly lower, with a value of 13 versus 48 in the control. Change in insulin relative to control was nonsignificantly lower at 4 units with the data as the control went up 2, and the test substance MCH went down 2 units. Insulin and glucose levels had a tendency to be lower in the MCH group, with glucose being about 17 units lower.
<b>Conclusion</b>	Lowering cardiac stress and muscle damage may be brought about by VPP and IPP, which would be able to induce vasodilatation and improve blood flow with increased NO level. Improved blood flow and cardiac muscle stress relief are benefits.

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Iwasa M, Aoi W, Nakayama A, et al. Milk casein hydrolysate alleviates muscle soreness and muscle fatigue after downhill walking exercise in middle-aged to elderly men. Poster presented at: 12th Asian Congress of Nutrition; May 2015; Yokohama, Japan.

<b>Topic</b>	What is the potential of the proprietary casein hydrolysate on muscle soreness and muscle fatigue in middle-aged to elderly men?
<b>Background</b>	A previous animal study has shown that <i>Lactobacillus helveticus</i> -fermented milk prevents muscle damage induced by acute exercise via activation of antioxidative enzymes of skeletal muscle. A subsequent human study on healthy young men further showed that the same fermented milk mitigated the elevation of creatine phosphokinase after 45 minutes of resistance training (leg press and bench press) compared with the placebo group. Self-report on pectoralis muscle soreness was also significantly lower than that of the placebo group. The present study investigated the effect of milk casein hydrolysate, which contains the same peptides as the <i>Lactobacillus helveticus</i> -fermented milk, on muscle soreness in middle-aged to elderly men.
<b>Study Type</b>	Human intervention study
<b>Study Design</b>	Randomized, placebo-controlled crossover design
<b>Subjects</b>	14 healthy middle-aged to elderly men
<b>Dosage</b>	Casein hydrolysate tablets (contains 3.4 mg of IPP and VPP) split into 2 servings, 30 minutes before and 30 minutes after a downhill walking exercise
<b>Results</b>	Fourteen subjects were randomly assigned to 2 groups for the trial, which lasted for 2 days. On day one, each group performed a 30-minute downhill exercise and took either a placebo tablet or hydrolyzed casein tablet 30 minutes before and after the exercise. They reported on femoral, crural, and gluteus maximus muscle soreness based on the visual analog scale (VAS). The hydrolyzed casein group consistently reported having less muscle soreness than the placebo group; the difference was significant at $p < 0.05$ for the femoral and crural muscle ratings (Wilcoxon signed-rank test). Fatigue was also assessed with the VAS and profile of mood state. The hydrolyzed casein group was significantly less fatigued than the placebo group at $p < 0.05$ (paired t-test).
<b>Conclusion</b>	Supplementation with milk casein hydrolysate that contains standardized lactotripeptides IPP and VPP alleviated muscle soreness and fatigue induced by downhill walking in middle-aged to elderly men.