Effect of milk tripeptides on blood pressure: a meta-analysis of randomized controlled trials
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CRD summary
The authors concluded that milk-derived tripeptides IPP and VPP (isoleucine-proline-proline and valine-proline-proline) had hypotensive effects in pre-hypertensive and hypertensive individuals. Although the review findings were consistent, the conclusions may require a degree of caution in interpretation due to methodological limitations in the review, such as the poor reporting of methods.

Authors' objectives
To evaluate the effect of milk-derived tripeptides isoleucine-proline-proline (IPP) and valine-proline-proline (VPP) on blood pressure in individuals with hypertension or pre-hypertension.

Searching
MEDLINE via PubMed, EMBASE, Science Citation Index and Cochrane Central Register of Controlled Trials were searched from inception to August 2007. Search terms were reported. Reference lists of relevant studies, meta-analyses and reviews were handsearched. The search was restricted to articles published in English.

Study selection
Randomised controlled trials (RCTs) of milk-derived IPP and VPP for hypertensive or pre-hypertensive individuals were eligible for inclusion, provided the intervention lasted at least four weeks. Parallel group and crossover trials were eligible.

The proportion of men in the included trials ranged from 25% to 100%. Mean or median participant age ranged from 42 to 75 years. IPP and VPP were isolated from casein by fermentation and administered as liquid or tablets for periods that ranged from four to 21 weeks, generally with a run-in period of one to four weeks. The IPP and VPP intake ranged from 2.6 to 5.6 mg/dL. Controls received sour or acidified milk or tablets as appropriate. Medical treatment of hypertension was an exclusion criterion in most RCTs. The review outcome was change in systolic and diastolic blood pressure; adverse effects were also reported. Most of the included studies were conducted in Japan and sponsored by a milk drink company; the other studies were conducted in Finland.

The authors stated neither how the papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
Study quality was assessed using the Jadad score to measure adequacy of randomisation, blinding and management of withdrawals and dropouts. Each study was awarded a score out of a maximum of 5 points. The authors did not state how the assessment was performed.

Data extraction
For each study, mean differences in blood pressure and their standard errors were calculated from the differences in blood pressure change between the intervention and control groups at the end of the intervention. If necessary, the standard error of the change was calculated from the within-group standard errors or standard deviation, the 95% confidence interval (CI) or test statistics. A correlation of 0.5 was assumed between variances at baseline and final measures. Two reviewers independently extracted the data; disagreements were resolved by consensus.

Methods of synthesis
Data were pooled statistically. Studies were weighted by the reciprocal of their variance for blood pressure change. Statistical heterogeneity was assessed using the $X^2$ statistic. If no statistically significant heterogeneity was present, a fixed-effect model was used; otherwise a random-effects model was used. Subgroup analysis was conducted to check whether effects differed by variables such as blood pressure status, run-in period and type of treatment. Publication bias
was assessed by visual scan of a funnel plot of systolic blood pressure changes and with Egger's regression test.

**Results of the review**

Nine parallel-group RCTs that reported 12 comparison groups were included in the review (n=623, range 17 to 144). Three RCTs stratified participants by blood pressure status. Nine comparison groups were double blinded and three were single blinded. All studies received a Jadad score of 4 or 5. Drop-out rates ranged from 5% to 10%. No RCTs reported use of intention to treat analysis.

When all 12 comparisons were pooled, IPP and VPP significantly reduced blood pressure compared to controls: systolic blood pressure reduced by -4.8mmHg (95% CI -6.0 to -3.7) and diastolic by -2.2mmHg (95% CI -3.1 to -1.3). There was no evidence of significant heterogeneity or publication bias.

Subgroup analysis showed a more marked effect in the hypertensive group than in the pre-hypertensive group; the difference (2.4mmHg) was statistically significant for systolic blood pressure. Other subgroup analyses showed no significant differences between groups.

Most RCTs reported minor adverse events in both groups, none of which were considered to be treatment related.

An additional analysis (apparently post-hoc) suggested a trend for effects to increase over follow up.

**Authors' conclusions**

Milk-derived tripeptides IPP and VPP had hypotensive effects in pre-hypertensive and hypertensive individuals.

**CRD commentary**

The objectives and inclusion criteria of the review were clear and relevant sources were searched for studies, although the restriction to published studies in English meant that the review may have been subject to language and publication biases. Formal tests showed no evidence of publication bias but, as the authors noted, the test may have been underpowered. Steps were taken to minimise the risk of reviewer bias and error by having more than one reviewer independently extract data; the processes for study selection and validity assessment were not described, so the potential for bias was unknown. Relevant criteria were used to assess some aspects of study validity, but the perfect Jadad scores obtained by most studies were undermined by their failure to report intention to treat analysis. Moreover, the review did not report on important aspects of quality such as allocation concealment. There were some inconsistencies in reporting in the review. Appropriate statistical techniques appeared to be used to combine the studies and assess for heterogeneity. Other potential limitations (such as questionable generalisability and commercial sponsorship) were acknowledged in the text. Although the review findings were consistent, the authors' conclusions may require a degree of caution in interpretation due to methodological limitations in the review, such as the poor reporting of methods.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further RCTs were needed to test the hypotensive effects of milk peptides. Studies should be conducted in a range of different countries and should be without commercial sponsorship. The appropriate dose of tripeptides to be used by both normal and hypertensive populations also needed to be determined.

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