Does Hypertension Protect Against Chronic Musculoskeletal Complaints?

The Nord-Trøndelag Health Study

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Background: Although an inverse relationship between pain sensitivity and hypertension has been described, it is still unknown whether hypertension may protect against chronic musculoskeletal complaints (MSCs). The aim of this study was to evaluate the relationship between blood pressure (BP) and prevalence of chronic MSCs at various anatomical sites.

Methods: Two consecutive public health studies within the county of Nord-Trøndelag, Norway, were conducted between January 5, 1984, and February 15, 1986 (Nord-Trøndelag Health Study [HUNT] 1), and from August 1995 to June 1997 (HUNT-2). Among 46,901 adults who participated in both surveys, 24,127 (51.4%) in HUNT-2 who reported MSCs continuously for at least 3 months during the past year were defined as having chronic MSCs. The prevalence of chronic MSCs was estimated using multiple logistic regression, with odds ratio and 95% confidence interval as measures of association with systolic and diastolic BP.

Results: A high systolic and diastolic BP was associated with a 10% to 60% lower prevalence of chronic MSCs, and there was a strong linear trend (P < .001) of decreasing prevalence of chronic MSCs with increasing BP values. The findings were remarkably consistent at all anatomical sites, for both sexes, across all age groups, and for systolic and diastolic BP measured in HUNT-1 and HUNT-2.

Conclusions: Individuals with a high BP had a lower prevalence of chronic MSCs than individuals with a normal BP. One possible explanation may be the phenomenon of hypertension-associated hypalgesia, due to an interaction between the cardiovascular and pain regulatory systems. The effect of antihypertensive medication on this interaction should be evaluated in further studies.

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We were also able to investigate how the relationship between BP and chronic MSCs was influenced by changes in BP and antihypertensive treatment.

METHODS

STUDY POPULATION

In the county of Nord-Trøndelag, Norway, 2 extensive public health studies have been performed (the Nord-Trøndelag Health Studies [HUNTs]). All residents of the county 20 years and older were invited to participate in the studies. In HUNT-1 (January 5, 1984, to February 15, 1986), the main topics were BP, diabetes mellitus, and health-related quality of life. Of 83 100 eligible individuals, 74 599 (87.7%) answered the questionnaire that was sent with the invitation and participated in a medical examination. A detailed description of the study population, including the participants and nonparticipants, has been published previously. In HUNT-1, no question about musculoskeletal symptoms was included. HUNT-2 (August 1995 to June 1997) was more extensive than the first survey, and 66 140 (71.2%) of 92 936 individuals participated. A total of 47 556 individuals participated in both studies. Overall, 63.5% of the invited individuals in HUNT-2 who were 30 years or older responded to the musculoskeletal questions and participated in HUNT-1. Of the 74 599 participants in HUNT-1, 14 599 (19.6%) had died or moved out of Nord-Trøndelag between HUNT-1 and HUNT-2.

In both surveys, BP was measured with the patient in a sitting position according to standardized methods described in detail elsewhere. In HUNT-1, a mercury sphygmomanometer was used, and BP was measured after at least 4 minutes of rest with the cuff placed on the right upper arm. The cuff was inflated twice, with an interval of at least 1 minute, and in this study, the second reading was used. In HUNT-2, the measurements were performed with an automatic oscillometric method (Dinamap 845XT; Criticon, Tampa, Fla). Blood pressure was measured after a minimum of 2 minutes’ rest in the sitting position, and 3 consecutive standardized BP measurements were recorded at 1-minute intervals. In this study, the mean of the second and third readings was used. Blood pressure readings measured using the automatic oscillometric method are slightly lower than those measured with a sphygmomanometer, especially for diastolic BP (DBP).

HUNT-2 included questions about musculoskeletal symptoms adopted from the Standardised Nordic Questionnaire, which has previously been evaluated and found to give reliable estimates for upper limb and neck discomfort and low back pain. Information about pain in other parts of the body has not been validated. All participants were asked: “Have you during the last year continuously for at least 3 months had pain and/or stiffness in muscles and joints?” Of the 47 556 persons who participated in both surveys, 46 901 (98.6%) responded, and 24 127 (51.4%) of these respondents who reported pain and/or stiffness for 3 months or longer during the past year were defined as having chronic MSCs. Individuals who reported chronic MSCs were asked to mark the localization of this pain (neck, shoulders, elbows, wrists/hands, chest/abdomen, upper back, lower back, hips, knees, and/or ankles/feet). The study was approved by the Regional Committee for Ethics in Medical Research and by the Norwegian Data Inspectorate.

STATISTICAL ANALYSIS

Differences between proportions were analyzed by the χ² test. P<.05 was considered statistically significant. The prevalence of chronic MSCs at 10 anatomical sites (dependent variable) was estimated using multiple logistic regression, with the odds ratio (OR) and 95% confidence interval as measures of association with BP (independent variable) in HUNT-1 and HUNT-2. For data presented in Figure 1 and Figure 2, BP was divided into categories using increments of 10 mm Hg (systolic BP [SBP], 8 categories; and DBP, 6 categories), but for data presented in Tables 1, 2, and 3, BP was divided into 3 categories (<140, 140-159, and ≥160 mm Hg for SBP and <90, 90-99, and ≥100 mm Hg for DBP).

We evaluated the influence of change in BP categories from HUNT-1 to HUNT-2 on chronic MSCs, using normotensive individuals in both surveys as a reference. For this analysis, we used the 3 BP categories previously mentioned, resulting in 9 different BP change categories for SBP and DBP (Table 3). Individuals with the most extreme change for SBP, for example, were those who had an SBP of 160 mm Hg or higher in HUNT-1 but an SBP lower than 140 mm Hg in HUNT-2. Potential confounding was evaluated by adjusting for age (5-year categories), years of education (3 categories: <10, 10-12, and >12 years), use of antihypertensive medication (yes or no), daily or almost daily use of analgesics (yes or no), current smoking (yes or no), alcohol consumption (3 categories), physical activity (4 categories), and body mass index. To evaluate the influence of use of antihypertensive medication on the relationship between BP and chronic MSCs, we repeated the analyses after excluding the 8578 individuals who used or had used such medication, as assessed from information collected in HUNT-1 or HUNT-2. In addition, the relationship between BP and chronic MSCs was evaluated in the restricted group of 6710 individuals who reported current use of antihypertensive medication. Finally, using individuals
without antihypertensive medication use and a low BP (SBP, <120 mm Hg; or DBP, <80 mm Hg) as a reference, the prevalence of chronic MSCs at different BP levels was calculated in those with and without current use of antihypertensive medication.

All potential confounding factors were included in the multiple logistic regression analyses separately or together, but were excluded from the final analyses if the OR changed by less than 0.1. Age, level of education, and use of antihypertensive medication were important confounders, and, therefore, all final analyses were adjusted for these factors. We also investigated potential interaction between use of antihypertensive medication and BP by including the product of the 2 variables into the logistic regression analyses. The interaction coefficients were tested using the Wald χ² statistic.

Where appropriate, BP was treated as a continuous variable and was incorporated in a 2-sided test for trend to evaluate the probability of a linear relationship between BP and chronic MSCs (dose-response relationship).

Statistical analyses were performed using a commercially available software program (SPSS, version 11.5; SPSS Inc, Chicago, Ill).

RESULTS

SYSTOLIC BP

A high SBP (≥150 mm Hg) measured in HUNT-1 was associated with a lower prevalence of chronic MSCs in HUNT-2 in all age groups, and for each sex, when using crude data (Figure 3). In multivariate analyses adjusting for confounders such as age, educational level, and use of antihypertensive medication, there was a strong linear trend (P<.001) of decreasing prevalence of chronic MSCs with increasing SBP (Table 1). The inverse relationship with chronic MSCs was evident for SBP measured in HUNT-1 and HUNT-2 (Table 1).

A high SBP was associated with a 20% to 60% lower prevalence of chronic MSCs at all 10 anatomical locations (Table 2). Among individuals with an SBP of 160 mm Hg or higher in HUNT-1, the prevalence OR of chronic neck pain was 0.6 compared with those with an SBP lower than 140 mm Hg (Table 2). The inverse relationship was most marked for pain in the trunk (back, chest, and abdomen) but was not significantly different from pain elsewhere (Table 2).

When the population was divided into 8 groups according to SBP levels, using individuals without antihypertensive medication use and an SBP lower than 120 mm Hg as a reference, the prevalence of chronic pain decreased almost linearly with increasing SBP from lower than 120 mm Hg to 180 mm Hg or higher (Figure 1). An inverse relationship between SBP and chronic MSCs was evident for both sexes, and for those without and with current use of antihypertensive medication. This tendency was also present after adjustment for a significant age difference. Based on the results shown in Figure 1, one could ask whether use of antihypertensive medication modifies the inverse relationship between chronic MSCs and SBP. Our results supported such an interaction between antihypertensive agents and SBP measured in HUNT-1 for men (P=.04) and in HUNT-2 for women (P=.01). This modifying effect of antihypertensive agents was illustrated in analyses comparing subjects with and without current use of such medication. For example, in women with an SBP of 160 mm Hg or higher measured in HUNT-2, the prevalence OR of chronic MSCs was 0.67 (95% confidence interval, 0.61-0.74) in those without use of antihypertensive medication (n=19,930), compared with 0.82 (95% confidence interval, 0.68-0.97) in those with current use of such medication (n=3811).

DIASTOLIC BP

Parallel trends were found for DBP measured in HUNT-1 and HUNT-2 (Table 1). When the population was divided into 6 groups according to DBP levels in HUNT-2, using individuals without antihypertensive medication use and a DBP lower than 80 mm Hg as a reference, the OR of chronic MSCs decreased for both sexes with increasing DBP (Figure 2). This trend was also evident for individuals using antihypertensive medication, except for DBP measured in men in HUNT-1. The prevalence of chronic MSCs tended to be highest among individuals with a low DBP and current use of antihypertensive medication (Figure 2), but no significant interaction was found between the use of antihypertensive agents and DBP in relationship to chronic MSCs.
For both studies, a high DBP was associated with a lower prevalence of chronic MSCs at all 10 anatomical locations (Table 2). For DBP measured in HUNT-1, this was most evident for women (data not shown).

**CHANGE IN BP FROM HUNT-1 TO HUNT-2**

Individuals with an elevated SBP or DBP in HUNT-1 and/or HUNT-2 had a lower prevalence of chronic MSCs compared with those with a normal BP in both surveys (Table 3). The lowest prevalence of chronic MSCs was found among those with a high SBP or DBP in both studies.

To our knowledge, this is the first large-scale population-based study investigating the relationship between BP and prevalence of chronic MSCs at various anatomical sites. The findings were remarkably consistent, demonstrating lower prevalence with increasing BP values. At all anatomical sites, for both sexes, and across all age groups, we found a dose-response relationship for SBP and DBP.

Our results are in accordance with those of a previous prospective study, which reported a lower head-
ache risk among individuals with a high BP. Similarly, a decreasing frequency of migraine with increasing BP has been found in 2 other studies.9,10

Table 3. Prevalence Data for Chronic MSCs (≥3 Months During the Past Year) in 46,075 Subjects Related to Change in BP Between HUNT-1 and HUNT-2

<table>
<thead>
<tr>
<th>BP, mm Hg</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>HUNT-1</td>
<td>HUNT-2</td>
<td></td>
</tr>
<tr>
<td>&lt;140</td>
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<td>21,808</td>
</tr>
<tr>
<td>&lt;140</td>
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<td>≥160</td>
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<tr>
<td>≥160</td>
<td>≥160</td>
<td>2,285</td>
</tr>
</tbody>
</table>

Abbreviations: See Table 1.
*There were 826 subjects with incomplete BP data in HUNT-1 and/or HUNT-2.
†The ORs were adjusted for age, education, and use of antihypertensive drug therapy.

The strengths of the study include the population-based design with high participation rates, reducing the risk of selection bias. The large sample size reduced the risk of chance findings and facilitated extensive subgroup analysis. The wide range of health-related information made it possible to adjust for potential confounding variables.

It is a limitation of our study, however, that no questions about MSCs were included in HUNT-1. Thus, we do not know whether MSCs may have influenced BP at baseline in HUNT-1. Furthermore, although the attendance rate was high, we cannot rule out the possibility of selection bias. Individuals who responded to the MSC questions were younger, more likely to be women, and had a higher socioeconomic status than the nonresponders. Thus, generalization of our results to those who did not participate must be done with caution.

Finally, the individuals who reported chronic MSCs were not asked questions about pain intensity. This may be important because highest resting DBP has been found in patients reporting the greatest clinical pain intensity.14 Possibly, the relationship between BP and pain may be less clear in individuals with chronic high-intensity MSCs than in those with low-intensity MSCs.

It could be argued that chronic MSCs were less frequent in subjects with a high BP because the symptoms were better treated among those with a tendency to hypertension because they probably visited physicians more often than normotensive subjects. However, this explanation seems unlikely because a consistent dose-response relationship was clearly demonstrated among those without use of antihypertensive medication.
Interestingly, our data indicated that use of antihypertensive agents modified the inverse association between chronic MSCs and SBP measured in HUNT-1 (men) and in HUNT-2 (women). In addition, increased pain sensitivity has been reported in hypertensive patients during treatment with antihypertensive medication.22

The inverse relationship between BP and prevalence of chronic MSCs was found at all 10 anatomical sites. The pain in these different sites probably has various local causes and mechanisms. Although the possibility cannot be absolutely excluded, it seems unlikely that a high BP should exert an effect on pain mechanisms at the site of the pain. Therefore, our findings probably reflect the effect of a fundamental relationship between BP and pain perception per se in the central nervous system. This phenomenon has previously been described as hypertension-associated hypalgesia.5,7 Low pain sensitivity has been reported in hypertensive animals and humans and in groups deemed to be at an increased risk for the development of hypertension.5,7 Of particular relevance to the results of the present study is that an inverse relationship between BP levels and sensitivity to painful stimuli extends into the normotensive range.23 The mechanism for hypertension-associated hypalgesia is not clear, but data from humans and rats suggest an interaction between the cardiovascular and pain regulatory systems. Because the relationship between BP and pain sensitivity is present even in the absence of clinical hypertension, it may reflect some common central mechanism underlying antinociception and cardiovascular regulation rather than a specific effect of hypertension itself.

A role for baroreceptors in mediating the BP–pain sensitivity relationship has received some experimental support.24 Endogenous opioid mechanisms have also been linked to the baroreceptors.25 It has been suggested that endogenous opioids are necessary for full expression of the relationship between resting BP and pain sensitivity and that endogenous opioid dysfunction could play a major role in the development of chronic pain.25 However, because opioid blockade has no significant effect on the BP–pain sensitivity relationship, it is still unclear whether this relationship is related to endogenous opioids.24

Other neurotransmitters, like catecholamines, may also be involved.2 The metabolism of catecholamines is affected by the COMT (catechol-O-methyltransferase) gene. It may be of relevance that a polymorphism of this gene has recently been shown to influence the response to pain26 and that the COMT gene may be important also for BP regulation.27

The results of the present study have many important consequences. Because BP seems to have a relatively strong association with chronic MSCs, it is important to consider this as a potential confounding factor in studies of patients with such complaints. If BP differs systematically between groups, differences in chronic MSCs may be expected and results should be adjusted for BP. Even more intriguing is that use of antihypertensive medication may have an influence on the BP–pain sensitivity relationship. The widespread use of such medication should motivate more detailed studies on how it affects pain sensitivity and whether it elicits or escalates pain in individuals starting to receive such medication.

In conclusion, our large population-based study provides evidence of an inverse relationship between BP and prevalence of chronic MSCs. From our study, it is evident that the mechanism responsible for the BP–pain sensitivity relationship has a substantial effect on chronic pain in the general population because there was a 10% to 60% decrease of prevalence among those with a slightly increased BP. This underlines the importance of determining these mechanisms in greater detail to increase our understanding of chronic pain and perhaps also of hypertension and its treatment.

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REFERENCES