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Original article

Chiropractic care for hypertension: Review of the literature and study of biological and genetic bases

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Abstract. *Background and aim:* Hypertension is a multifactorial condition that is among the leading causes of mortality worldwide. Regulation of blood pressure greatly depends upon the activity of the autonomic nervous system. Alterations in the autonomic nervous system can lead to hypertension. In addition to nervous system control and individual physiologic state, various genes can directly influence autonomic responses. The complexity of blood pressure control is reflected in the 20-30% of individuals resistant to traditional pharmacological treatment, this indicates the need for alternative interventions. This article provides an integrative review and discussion of the key neurophysiologic and genetic factors that contribute to blood pressure regulation, the autonomic nervous system (ANS) and manual therapy literature, and the manual therapy and blood pressure literature. *Methods:* To assess the effects of chiropractic on the management of hypertension we searched articles published from 1980 to 2019 in PubMed, the Index to Chiropractic Literature and CINAHL, using the keywords: chiropractic, spinal manipulation, hypertension, and blood pressure. *Results:* We found 38 original studies that analyzed the effect of chiropractic therapy on hypertension. Of these studies, 10 were case reports and the statistical significance of the effects of chiropractic on blood pressure was not evaluated on these articles, so we focused on the remaining 28 articles. *Conclusions:* The results of the review relative to chiropractic care were promising, but often contradictory, suggesting more research should be done. In consideration of the complexity of ANS blood pressure control, an evaluation of patient presenting physiologic and genetic characteristics is recommended and could provide valuable insight relative to the likelihood of patient blood pressure related responsiveness to care (www.actabiomedica.it)

Key words: hypertension, autonomic nervous system, spinal manipulative therapy, chiropractic manipulative therapy, sympathetic response, parasympathetic response

Introduction

Hypertension (high blood pressure) is a common multifactorial disorder that results in high morbidity and mortality around the world (1). According to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, hypertension is defined as systolic blood pressure of 140 mmHg or above with diastolic blood pressure of 90 mmHg or above (2).

Although recent advancements enable us to better understand the etiology of hypertension and provide new treatment options, the prevalence of hypertension is increasing. Globally, almost 26% of the adult population is experiencing hypertension at present, and according to an estimation by Kearney et al, the prevalence will increase to 29% by 2025 (3). Adding to the complexity of the challenge, almost 90% of hypertensive cases are of essential (primary, with an unknown etiology) hypertension, which is the 13th significant cause of mortality in the United States (4).

As a multifactorial condition, there are a number of risk factors associated with the development of primary hypertension. Genetics, for example, have been

shown to play a major role in the onset of hypertension, along with other factors such as sex, age, weight, diet, stress, physical activity, hormones and cigarettes smoking (4). However, the effect of genetics, weight, diet or other risk factors as singular causes of hypertension is less supported (5). Emerging research suggests that the etiology or foundational susceptibility of an individual to the development of hypertension may be associated with dysfunctional regulation of the autonomic nervous system (ANS), particularly to the abnormal activation of parasympathetic and sympathetic systems (6-8). A review by Grassi showed that an increased sympathetic drive may serve as an amplifier or determinate of elevated blood pressure and its associated effects (9). Interestingly, a number of genetic variations associated with high blood pressure are also involved in changes to sympathetic control (10-13). The association between high blood pressure and aberrant autonomic control is important because it provides a gateway for therapeutic intervention, especially because many pharmaceutical approaches directly target or mimic autonomic nervous system responses (14).

There are two main challenges to pharmacotherapy for hypertension, therapeutic resistance and medication side effects (15-18). Resistant hypertension - defined as individuals who fail to reach their target blood pressure despite being on three concurrent medications at prescriptive doses, with one medication being a diuretic – is present in 20-30% of hypertensive individuals (15,19-20). Further, this population presents with greater risk of health complications and mortality (15,19,21-22). Relative to medication side effects, they range from mild, such as dizziness, headaches, electrolyte imbalance, and cough to more serious events including erythema multiforme major, heart palpitations, increased creatinine, vasovagal syncope, and renal impairment (16-18). Given the rise in hypertensive cases and the challenges to pharmacotherapy, alternative interventions with limited risk should be explored, and further examination of therapies such as chiropractic - shown to influence the ANS - could be a likely candidate (2,16-18,23-25).

Chiropractic care as a therapeutic intervention for blood pressure regulation is not a new concept, although the research examining blood pressure changes following care does not consistently provide support (26-29). This inconsistency could be the result of the complexity of neurophysiologic control of blood pressure regulation and/or genetic variability. The aim of this article was not to conduct a formal systematic review, but to discuss the literature from an integrative perspective and highlight the need for additional outcome assessments (e.g. genetic predisposition), following three topics: key neurophysiologic and genetic factors that contribute to blood pressure regulation, the ANS and manual therapy literature, and the manual therapy and blood pressure literature.

Regulation of blood pressure

Arterial blood pressure is primarily regulated by the ANS, which comprises the parasympathetic and sympathetic nervous systems (6,30). These two systems are counterbalanced and constantly regulate and control blood pressure through receptor-based feedback loops (30). Although it is acknowledged that cortical control of blood pressure is a factor, as evidenced by elevated blood pressure while in a doctor's office (white coat syndrome) and meditation-based blood pressure control, this article will focus on two receptor-based ANS control mechanisms, the baroreceptor response and the renin-angiotensin-aldosterone system (RAAS) (31-34).

Autonomic Nervous System Regulation

Alterations of ANS activity have a direct role in the onset and development of human hypertension (6,30,35). The increase of sympathetic nervous system activity and the reduction of vagal cardiac tone are associated with the onset and persistence of hypertension (6,36).

Interestingly, both sympathetic and parasympathetic divisions of the ANS might present with abnormal activity in individuals with higher hypertension risk, even before the onset of any clinical signs (30,37,38). Patients in the early stages of hypertension have amplified sympathetic and decreased cardiac vagal (parasympathetic) activities (30,37,39). A review by Mancia and Grassi showed marked alterations in ANS control in prehypertensive, early hypertensive,

and established hypertensive states (30). Decrease in cardiac parasympathetic nervous system activity, estimated by the analysis of heart rate variability, has also been shown to increase mortality rate (40). Further, according to animal studies, alterations of the sympathetic system cause observed inter-individual variability of blood pressure (35). This is confirmed in adult rats, spontaneously hypertensive, that show reduction in cardiac parasympathetic nervous activity, accompanied with increased sympathetic nerve activity and elevated noradrenaline release (41).

Baroreflex

The baroreflex has the ability to buffer the acute changes of arterial pressure (42). The buffering of blood pressure is usually mediated by the parasympathetic and sympathetic regulated heart rate and the sympathetic vasomotor tone modulation (43). The heart rate and the sympathetic nervous system activity are regulated by cardiovascular baroreceptors.

Baroreceptors are mechanoreceptors that increase action potential firing in response to the widening and stretching of the blood vessels (44). The acute changes of blood pressure are regulated by the baroreceptors located in the blood vessels and heart, in particular the high-pressure receptors located in the aortic arch and carotid sinuses (44,45). Baroreceptor activation during elevated blood pressure efficiently inhibits the response of efferent sympathetic nerves and increases the efferent vagal activation on the SA node of the heart. This vagally mediated response leads to release of acetylcholine and inhibition of the SA node – decreasing the heart rate (44,45). Concurrently, the sympathetic mediated norepinephrine release on the SA node is diminished, further decreasing the SA mediated heart rate. As an additional consequence of diminished sympathetic outflow, sympathetic vasomotor tone is decreased, allowing vascular dilation within the venous and arterial systems. The decreased vasomotor tone decreases total peripheral resistance and alters end diastolic and systolic volumes, leading to a decrease in blood pressure (44,45).

The sympathetic and parasympathetic responses are in reverse when stretch on the mechanoreceptors is diminished, as in the case of low blood volume or blood pooling in response to gravity-dependent positional changes (46). The baroreceptor reflexes provide immediate, acute responses to changes in blood pressure or volume. Subsequently, the efferent activities of the sympathetic and parasympathetic nervous systems are readily adjusted to stabilize the blood pressure. Baroreflex afferents are also known to regulate the release of vasopressin from the hypothalamus, which is considered a backup mechanism for the stabilization of blood pressure (43).

Functional loss of the afferent baroreflex leads to baroreflex failure, characterized by unstable arterial hypertension (46). Alternatively, the functional loss of the efferent baroreflex causes autonomic failure linked with intense orthostatic hypotension (46). Although the baroreceptor response is classically adapted for acute homeostatic control, failure or adaptation of the responses can have implications in chronic blood pressure regulation (46,47). In humans, essential hypertension is associated with impaired regulation of heart rate and sympathetically mediated vasomotor tone (30,37,43).

To evaluate the effects of baroreflex failure, the degree of response of the target organs - especially the kidneys - towards the reset of baroreflex control of sympathetic nervous activity helps to establish the levels of the long-term blood pressure and progression of hypertension (43). The changes in sympathetic nervous activity of the kidney, mediated by the baroreflex, might affect the renin-angiontensin-aldosterone system (RAAS) and might also play a role in long-term changes of mean arterial blood pressure through the regulation of humoral factor levels that are active in autonomic regulation (42).

Similar to other mechanoreceptors, such as those in the skin that allow desensitization to clothing or watches, baroreceptor resetting occurs. Baroreceptor resetting might contribute to the development of hypertensive states (48,49). The normalization of baroreceptor sensitivity and the re-establishment of the baroreceptor pressure threshold is considered a promising therapeutic target for blood pressure control. Patients could possibly improve their blood pressure control by the use of novel therapeutic options that restore baroreceptor function and ANS responsiveness (42,48,49).

Renin-angiotensin-aldosterone system (RAAS)

The renin-angiotensin-aldosterone system (RAAS) by interacting with the autonomic nervous system regulates the blood pressure (50). This system comprises several hormones that increase blood volume and peripheral resistance. The RAAS is activated in response to decreased blood volume, increased sodium, or activation of the sympathetic nervous system, which initiates renin synthesis and release by the juxtaglomerular cells (32). Renin exerts its activity by entering the blood and interacting with angiotensinogen, produced by the liver. Then, renin converts the angiotensinogen into angiotensin I. Subsequently angiotensin I moves to the pulmonary vessels where the angiotensin-converting enzyme (ACE), produced by the endothelium, is converted into angiotensin II. While the lung endothelial tissue is considered the primary converter of angiotensin I to angiotensin II, it should be noted that ACE is produced and can exert effects within other tissues of the body, including the brain, kidneys, and cardiac tissue (51-54). This complicates pharmacologic based therapies such as ACE inhibitors (51,52).

Angiotensin II influences blood pressure through several different pathways. To increase blood volume, resorption and retention of water is increased through sodium resorption in the kidneys. This is accomplished in the proximal tubule of the kidney by angiotensin II and through angiotensin II effects on the zona glomerulosa of the adrenal glands. This leads to release of aldosterone from the adrenal glands, which acts on the late distal tubule and collecting duct of the kidney nephron (55). Additionally, angiotensin II receptors on the hypothalamus increase the sense of thirst, prompting the individual to take in more fluids, increasing blood volume further. Through increased fluid volume, blood pressure rises (55,56).

Angiotensin II also activates and works in concert with the sympathetic nervous system to cause vasoconstriction. This is accomplished through angiotensin II receptors directly on blood vessels and stimulation of post-ganglionic sympathetic neuron release of norepinephrine (57). Vasoconstriction leads to increased total peripheral resistance and changes in cardiac output, increasing blood pressure (58). Although potentially more of a target for pharmaceutical interventions, the involvement of the sympathetic nervous system in initial stimulation of the RAAS and responsiveness to angiotensin II may provide a gateway for interventions that specifically affect the sympathetic nervous system, such as chiropractic (59-62).

Genetic bases of the regulation of the vascular resistance regulated by the autonomic nervous system

Resting blood pressure is greatly affected by genetic variability, and over 1500 genes influence the blood pressure. Several studies have explored the impact of different SNPs on the variability of blood pressure and heart rate within each individual. Genetic factors are estimated to contribute for almost 30-50% of the resting blood pressure levels (63). Similarly, twin studies showed that systolic and diastolic blood pressure levels have an heritability of 50-60%, and monozygotic twins have higher heritability than the dizygotic twins. Furthermore, blood pressure concordance is higher among biological siblings than in the adopted ones that live in the same environment. Finally, hypertension shows population-specificity in the interactions between gene and environment (12). The genetic polymorphisms associated with hypertension are found in genes involved in the following mechanisms: catecholaminergic metabolic and signaling pathways, ANS activity regulation, and baroreflex (Table 1).

Catecholaminergic signaling pathways

Most of the genes involved in hypertension participate in the catecholaminergic metabolic and signaling pathways. In a study performed by Krushkal et al., the region containing *ADRB2* gene is associated with the systolic blood pressure in young Caucasians. In subsequent studies, it was found that two polymorphisms (Gln27Glu and Arg16Gly) in *ADRB2* influence the inter-individual blood pressure variability and the onset of hypertension (13).

Another adrenergic receptor encoded by the gene *ADRA1A* has several polymorphisms that show association with blood pressure in Brazilian, Caucasian and African-American populations (64). One of these polymorphisms is the Arg347Cys with the Cys/Cys genotype that is associated with hypertension (64).

Table 1. Genetic polymorphisms associated with hypertension

Gene	Polymorphisms	Association with HT	Reference
TH	rs6356, rs10770141, $(TCAT)_n$	Sympathetic function, blood pressure	68
BDKRB2	-58C>T, rs1799722	Baroreflex sensitivity in never-treated hypertensive patients	76
GNB3	825C>T, 1429C>T, 5177G>A	Increased intracellular signal transduction, essential hypertension	72
ADRB2	Arg16Gly, Gln27Glu	Arterial blood pressure	72
ADRA1A	Arg347Cys	Essential hypertension	72
SLC6A2	rs168924	Essential hypertension	72
GNAS	393T>C, FokI(+/-)	Hypertension through dysfunctions of the ANS	74
AGT	M235T	Interaction with the ANS in the regulation of blood pressure and cardiovascular function	50
AGTR1	A1166C	Interaction with the ANS in the regulation of blood pressure and cardiovascular function	50
AGTR2	A1675G	Interaction with the ANS in the regulation of blood pressure and cardiovascular function	50
TRPV1	rs222747	Contribution to BP differences during static exercise	12
GCH1	+243C>T	Diastolic and systolic blood pressure	73
DBH	-970C>T, -1021C>T, -2073C>T	Essential hypertension	69
PNMT	rs876493, rs3764351	Blood pressure regulation	71
COMT	-1187G>C, rs4680	Essential hypertension	72

The adrenergic transporter encoded by the gene *SLC6A2* has a wide distribution along the nervous system, specifically in neuronal plasma membranes of noradrenergic neurons. *SLC6A2* gene plays a significant role in the re-uptake of adrenalin and noradrenalin. The SNP rs168924 has been found associated with essential hypertension (65).

The *TH* gene encodes the tyrosine hydroxylase, a rate-limiting enzyme that contributes in tyrosine conversion to dopamine and that plays an important role in the physiology of the adrenergic neurons. A study performed on a large general population sample proposed a relationship between the SNP rs10770141 near the *TH* promoter region and blood pressure (66). Other polymorphisms within the *TH* gene that are associated with blood pressure include a tetranucleotide repeat $(TCAT)_n$ located in the first intron of *TH* gene that is a strong determinant of baroreceptor slope, while the Val81Met polymorphism (rs6356) is associated with essential hypertension (67,68).

DBH gene encodes the dopamine β-hydroxylase enzyme which is an oxidoreductase that belongs to the copper type II, ascorbate-dependent monooxygenase family. The main function of this protein is to catalyze the dopamine conversion into norepinephrine, which functions as a neurotransmitter of sympathetic nervous system. Interestingly, in essential hypertension patients have an elevated level of DBH protein (66). Two polymorphisms of *DBH*, -2073C>T and -970C>T, are associated with essential hypertension (69).

Comparative genomics analyses have identified a gene locus that might be associated with blood pressure regulation in stroke-prone spontaneously hypertensive rats corresponding to the *PNMT* gene in human (70). *PNMT* gene encodes phenylethanolamine N-methyltransferase enzyme which methylates the norepinephrine in order to form epinephrine, during the last step in the biosynthetic pathway of catecholamine. According to further studies in the promoter region of *PNMT* two SNPs rs3764351and rs876493 were genotyped, within three ethnic populations including White Americans, African American and Greek white population, and their results proposed that in some populations the genetic variants of

PNMT gene might contribute in essential hypertension onset. Furthermore a research performed in Han Chinese population confirmed that the AA haplotype of SNPs rs3764351 and rs876493 have a protective effect in that population (71).

COMT gene encodes the catechol-O-methyltransferase enzyme, which is an important enzyme involved in norepinephrine metabolism that plays a key role in the norepinephrine plasma levels regulation. The SNP -1187G>C is associated with essential hypertension in Japanese men, while the SNP rs4680 is associated with hypertension in Swedish and Norwegian men (72).

The *GCH1* gene encodes the GTP cyclohydrolase 1 enzyme. This enzyme is involved in the biosynthesis of two central components of the pathophysiology of hypertension, catecholamines and nitric oxide. In particular, the SNP +243C>T influences the diastolic and systolic blood pressure in females (73).

ANS activity regulation

Among several molecular pathways ANS is regulated by G protein-coupled receptor pathways. G proteins are a family of proteins involved in transmitting signals from a variety of external stimuli. G proteins function as heterotrimers located within the cells and are activated by G protein-coupled receptors that span through the cell membrane. G protein-coupled receptor and G proteins work together for the transmission of signals from hormones, neurotransmitters, and other signaling factors. Functional variantions in these G proteins are associated with variation of ANS.

The *GNAS* gene encodes the G_s-protein α-subunit that is associated with the activity of ANS. The *GNAS* gene polymorphism T393C is associated with hypertension, and it might be a used as a genetic marker for the prediction of the onset of hypertension (74). Another common silent polymorphism, that causes the loss of a restriction site (FokI+/-) has been found associated with hypertension and with the response to the beta-blockers for the reduction of blood pressure (72).

GNB3 gene encodes a G-protein β subunit-3. Two polymorphisms, C1429T and C825T, are associated with essential hypertension in Turkish subjects. In fact, the 1429T and 825T variants have a significantly higher frequency in hypertensive patients as compared to the control group (75). Another research found that there is a 50% increased risk of hypertension for subjects that carry the 825T allele (72).

Baroreflex

Sympathetic nervous system activation is fundamental for maintaining blood pressure to normal levels and the functional differences in the muscle metaboreceptors chemical sensitivity could regulate the afferent feedback to the brainstem regions that control the efferent sympathetic and parasympathetic outflow which ultimately regulates blood pressure.

Bradykinin receptor B2 (*BDKRB2*) gene encodes the G-protein coupled receptors for bradykinin protein. Bradykinin protein performs several functions including stimulation of smooth muscle spasm and vasodilation. In a study including 129 mild and moderate hypertensive patients never treated, the association of *BDKRB2* gene polymorphic variant -58T>C has been reported for the autonomic-regulated baroreflex sensitivity (76).

Another research study including 200 healthy women and men disclosed that the variant in *BDKRB2*, rs1799722, together with the variant in the vanilloid receptor gene, *TRPV1*, rs222747, contribute in additive manner to the differences in blood pressure during static exercise (12).

Activation of sympathetic and parasympathetic systems through chiropractic care

Research studies on the effects of spinal manipulative therapy suggest that chiropractic care may influence the autonomic nervous system (24,25,77). Outcomes such as heart rate variability (HRV) and skin conductance have been shown to change following a chiropractic adjustment or osteopathic manipulation (24,25,78). HRV, an evaluation of consecutive beat-to-beat intervals of the heart, is a surrogate for extrinsic control of the heart through the ANS (24). A systematic review by Borges et al. that examined the osteopathic and chiropractic literature found that spinal manipulation of the cervical and lumbar regions tended to illicit a greater parasympathetic response,

whereas manipulation of the thoracic regions tended towards sympathetic activation as assessed by HRV (24). This makes sense in light of the location of the anatomic pathways of the nerves for the ANS.

The parasympathetic nervous system originates from brainstem nuclei and the sacral spinal cord. The brainstem preganglionic parasympathetic fibers exit through the following cranial nerves: oculomotor (III), facial (VII), glossopharyngeal (IX), and vagus (X) (79-81). Sacral preganglionic parasympathetic fibers leave the spinal cord from sacral nerves 2, 3, and 4, joining to form the pelvic splanchnic nerves (80,81). Although the cranial nerves and sacral fibers have multiple functions within the body, of relevance to the present article are the afferent and efferent control mechanisms for heart rate and the sympathetic inhibition (6,9,80,81). Although a mechanism of action to account for the autonomic changes following a chiropractic adjustment has yet to be fully developed, the anatomic proximity of the parasympathetic nerve fibers to the cervical and sacral spinal segments and the location-based HRV changes further support a location-dependent autonomic response (25,79-81).

In contrast to the parasympathetic nervous system, pre-ganglionic sympathetic neurons with cell bodies in the lateral horn of the spinal cord exit anteriorly and enter the anterior rami of T1-L2 spinal nerves (80,82,83). Some preganglionic nerves synapse with postganglionic neurons in a series of paravertebral ganglion (sympathetic chain ganglia) that span the entire spinal column, whereas others pass through the chain ganglia. The sympathetic nerves passing through the ganglia ascend or descend the sympathetic chain or leave the chain ganglia to synapse at different levels of the sympathetic chain or within prevertebral ganglia, respectively (80,82,83). The sympathetic nervous system innervates nearly every tissue of the body. Relative to the cardiovascular system, the sympathetic nervous system increases the heart rate, leads to activation of the RAAS system, and influences the vascular tonic state (6,80,82,83). In addition to HRV, another non-invasive way to measure sympathetic response is through measurement of the changes in skin conductance following application of a constant low voltage (84). A research, including a review and meta-analysis by Chiu et al, has shown that skin conductance can change in response to manual therapy, suggesting an increase in sympathetic nervous system activity (78,85-87).

The increased skin conductance – indicating increased sympathetic nervous system activity – results are different from the HRV location-dependent (cervical – parasympathetic increase; thoracic – sympathetic increase) manual therapy results (24,85). In alignment with the HRV results, thoracic stimulation through manual therapy indicated an increased sympathetic response; however, manual therapy to the cervical spine also indicated increased sympathetic response, contrary to the decrease observed in HRV (85). This complicates the logical anatomic relationship results shown with HRV and could be a result of the types of administered manual therapy, specific cervical vertebrae receiving manipulation, and complexity of the ascending and descending sympathetic nerve fibers. For example, in the Vicenzino study showing increased skin conductance, the therapeutic intervention was an oscillatory, lateral glide mobilization of the C5/C6 vertebrae (86). Whereas in the Welch et al. study showing increased parasympathetic response using HRV, an unspecified cervical adjustment was made in the supine position using the diversified technique (62). The diversified technique is often associated with a high-velocity low amplitude thrust (62). This inconsistency in force location and application may contribute to the inconsistent results observed in location dependent autonomic responsiveness between HRV and electrodermal responses. The inconsistency of outcome responses related to the adjusted spinal region is mirrored in the chiropractic blood pressure literature (26-29). These variations underscore the complexity of the blood pressure control mechanisms and the need for more research to understand the impact on autonomic control and the effects of presenting participant phenotypic and genotypic characteristics.

Methods and results

Chiropractic therapeutic application for hypertension

To assess the effects of chiropractic on the management of hypertension we searched articles pub-

lished from 1980 to 2019 and found 37 original studies that analyzed the effect of chiropractic therapy on hypertension (Supplementary Table 1) (23,28,29,62,88-120). The articles were pulled from PubMed, the Index to Chiropractic Literature and CINAHL, using the keywords: chiropractic, spinal manipulation, hypertension, and blood pressure. Of these studies, 10 were case reports; the statistical significance of the effects of chiropractic on blood pressure were not evaluated on these articles. Of the remaining 27, 13 did not report any significant changes in blood pressure and 14 studies showed significant changes in blood pressure after chiropractic intervention (23,28,29,62,88, 0-92, 94,95,97,99,100, 04,105,107-112,115-120). The cohorts of these 27 studies ranged from 11 to 331 individuals.Spinal manipulations were applied to the cervical spine in 16 of the 27 studies (23,28,29,62,88, 90-92,94,95,97,99,100,104,105,107-112,115-120). Ten of the studies showed significant changes in blood pressure following spinal adjustments, with 6 showing no significant differences or trends only (28,62,88,90-92,94,95,100,104,105,107,110-112,119). This difference in results could be attributed to many factors. For example, several of the significant results were observed through use of specific, low force upper cervical techniques such as Atlas Orthogonality or NUCCA (28, 62,88,90-92,94,95,100,104,105,107,110-112,119). While the Toggle study by Goertz et al. - not showing a significant difference in BP - also focused on the C1 or C2 vertebrae, this technique included a drop of the headpiece that the participant rested their head on for application of the adjustment (107). This could have had implications relative to local or regional nervous system effects. The results of the cervical BP studies are in alignment with the HRV research showing changes in the parasympathetic nervous system activity following cervical manipulations; however, the results are contrary to the skin conductance autonomic research which showed sympathetic stimulation following cervical and thoracic manipulation (24,78,85-87).

The 6 studies evaluating blood pressure changes with thoracic manipulations exhibited contradictory results relative to benefits of thoracic spinal manipulations on BP (23,62,99,117,118). The two studies demonstrating a decrease in BP following chiropractic care were in hypertensive patients and both utilized instrument adjusting (23,99). Only one of the three studies showing no significant difference included hypertensive patients; the two other study participant groups were non-hypertensive (62,117,118). All studies showing no change in BP utilized manual manipulative procedures (62,117,118). Interestingly, none of the thoracic BP studies showed an increase in BP, which would be expected based on the sympathetic nervous system and spinal manipulation research (24,25,78,85-87). Both HRV and electrodermal responses showed elevated sympathetic activity following a thoracic adjustment, basic physiology would suggest that the elevated sympathetic response would increase blood pressure (6,24,25,78,85-87). This increase was not reflected in the BP and manual therapy literature, exempting a small study by Wickles that showed slightly elevated BP in the ankle (23,62,99,115,117,118).

Finally, the full-spine and lumbar manipulation and BP literature showed mixed results similar to the thoracic manipulation results (29,97,108-110,115,116). The one lumbar only manipulation study by Younes, which employed osteopathic HVLA thrusts, mobilization, and muscle work, did not show a significant difference in blood pressure (116); however, the care did show a significant response to parasympathetic responsiveness through evaluation of the baroreceptor response (116). Of the research studies utilizing a full-spine approach, three showed changes in blood pressure and three did not (29,97,108,109,116,120). This could be related to several factors. For example, application of force at multiple different sites could have triggered both parasympathetic and sympathetic systems, complicating physiologic responsiveness. Additionally, the types of manipulative techniques varied from osteopathic manipulation and Gonstead chiropractic in the no significant change studies to chiropractic diversified adjustments and the McTimoney chiropractic method in studies demonstrating significant changes post care (29,97,108,109,116,120).

The variation in results and methodologies employed in the research of spinal manipulative therapy for blood pressure limit any conclusions that could be made relative to chiropractic or other manual therapy techniques and the effect on blood pressure. This suggests that more research is needed. The research utilizing adjustments to the cervical spine more consistently

demonstrate decreases in BP following manipulative therapy (28,62,88,90-92,94,95,100,104,105,107,110-112,119). The anatomic, HRV and electrodermal literature seem to support the cervical spine as an intervention point to influence the autonomic nervous system, although the electrodermal research seems counter to the HRV literature relative to which autonomic system is activated (24,25,77,78,85-87). One cervical manipulation and HRV study by Budgell et al. does show an increase in low frequency response, which is often attributed to sympathetic activation; however, increased sympathetic activation would suggest a blood pressure increase (121). This further illustrates the complexity of the intervention-response research and may indicate the need for improved understanding of the underlying neurophysiology related to BP control, location dependent nervous system responses to manipulative therapy, and participant characteristics prior to study onset.

Discussion and conclusions

Hypertension is a multifactorial disease, strongly dependent on the responsiveness of the ANS (6,30). This responsiveness depends on the integrity of the afferent and efferent pathways, sensory end organ reactivity, and interactions with systems such as renal and cardiovascular (6,9-11). These interactions produce short- and long-term adaptations to changes in the internal and external environment, creating complex feedback loops such as the baroreceptor reflex and the RAAS (6,9-11,32,42,43,50). Further, individual genetic predisposition also provides a complicating layer to the control of hypertension (63). Given the complexity of BP control, it is not surprising that pharmacotherapy, the primary mechanism for controlling blood pressure, has a 20-30% incidence of resistant hypertension (15,19,20).

The aim of this article was to summarize some of the physiologic and genetic bases of hypertension and review the chiropractic and manual therapy literature related to autonomic regulation and blood pressure control. This may provide a starting point for examining the efficacy of chiropractic as a therapeutic intervention to fill the gap in the need for treatment of hypertension, especially resistant hypertension, and could inform future study design in this area.

The results of the present review were mixed. While the research examining manual therapy to the cervical spine were the most supportive of chiropractic care as an intervention to lower blood pressure, evaluation of the ANS responses to cervical manipulation were only supportive in the HRV literature (24,25,77,78). The inconclusiveness related to manual therapy as a proposed intervention for blood pressure regulation has also been supported in other literature reviews (26,27,122). A review by Mangum and colleagues suggests that more low bias research is needed in order to draw conclusions relative to the effectiveness of chiropractic care for the hypertensive patient (27). As part of the UK Evidence Report and an evaluation of the effect of chiropractic treatment on primary and early secondary prevention of disease, reviews by Bronfort et al and Goncalves et al, respectively, further suggested a lack of evidence in support of chiropractic as a suggested care modality for hypertension (27,122).

While the aim of the present article was to provide a multi-perspective overview of hypertension and blood pressure regulation, the review was limited by the lack of a formal grading system for the blood pressure and autonomic literature. However, the less rigorous nature does provide an expanded perspective that raises more questions about the need for additional research. Some studies used normotensive patients, others used hypertensive patients at varying levels of hypertension, and others had a too small sample size to draw definite conclusions. Further, many studies utilized students as a convenience sample, which may be a challenge due to the stress induced by academics. Previous research also did not take into account genetic predisposition. Individual genetic background can have effects on regulation of the sympathetic and parasympathetic tone, which could impact the responses to chiropractic therapy (63). One example is the *GNAS* gene, encoding the G_s-protein αsubunit, associated with the activity of ANS and its polymorphism T393C, associated with hypertension (74). Additionally, studies examining the effects of chiropractic care on ANS activity demonstrated inconsistencies related to HRV, electrodermal responses, and predicted blood pressure responses (42,43,50). This illustrates

the complexity of therapeutic intervention development and study of hypertension.

Uniquely, this overview provided a brief introduction to some of the complex physiologic and genetic factors that comprise the multifactorial control of blood pressure and regulation of hypertension. The results of the review of manual therapy literature related to ANS responses and blood pressure were promising, but often contradictory. In some cases, although the lowering of BP was statistical significant, it was not clinically significant, in other cases the effect was short-term. This suggests that more research should be done and that consideration of the complexity of ANS control and patient presenting physiologic and genetic characteristics would be valuable. With further research, these presenting characteristics may help to serve as a predictor for patient blood pressure responsiveness to chiropractic care.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Table S1. Brief description of research studies investigating the effects of chiropractic therapy on hypertension

First author, year	Participants	Study design	Control group	Type of CMT	Results	Limitations
Bakris et al 2007[88]	50 patients with stage 1 hypertension subdivided in treated (25) and controls (25)	Double blind, placebo controlled. Duration: 8 weeks	Treatment vs placebo	Atlas/Upper cervical chiropractic adjustment	Systolic BP (treatment: -17+/-9 mmHg vs placebo: -3+/-11 mmHg, P<0.0001) Diastolic BP (treatment: -10+/-11 mmHg vs placebo: -2+/-7 mmHg, P=0.002). No adverse effects recorded	Should be confirmed in a larger trial
Torns 2012[90]	42 patients subdived in 3 groups: 12 hypotensive, 12 normotensive, 18 pre-hypertensive or stage 1 or stage 2 hypertensive	Cohort study. Duration: 1 treatment	Pre-treatment vs post-treatment	Atlas orthogonal upper cervical adjustment	Hypotensive group: systolic BP (+13.83mmHg, p<0.0001); diastolic BP (+8.83, p=0.0003). Normotensive group: systolic BP (-3.92, p= 0.1107); diastolic BP (-1.58, p=0.2486). Pre-hypertensive + hypertensive groups: systolic BP(-20.22mmHg , p<0.0001); diastolic BP (-6.83mmHg, p<0.0001). No adverse effects recorded.	Absence of a specific control group. Follow-up measurements did not measure the duration of the effects
Torns 2014[91]	20 participants (10 placebo group, 10 therapeutic group)	Placebo-controlled, randomized, prospective longitudinal cohort study. Duration: 6 weeks	Controls vs treatment	Atlas orthogonal upper cervical chiropractic care	Systolic BP (-12.2mmHg, p<0.05); Diastolic BP (-7.2; p<0.05)	The effect on the diastolic values were not significant after 4 weeks
Ward et al 2012[92]	48 normotensive college students (24 controls, 24 treated)	Single blind, randomized controlled trial. Duration: 24h	Controls vs treatment	Atlas cervical break	No significant differences before and after chiropractic care compared to head turn and no contact control	Non-hypertensive patients
Knutson 2001[94]	110 patients (80 in test one, 30 in test two)	Comparison study	Test 1: controlled clinical trial with a treatment group and a control group. Test 2: controlled clinical trial with subjects as controls	Vectored upper cervical care	Test 1: Significant decrease in systolic blood pressure (p<0.001); Test 2: No significant decrease in systolic blood pressure	Lack of randomization, blinding, manipulated control group
Kessinger et al 2019[95]	130 patients subdivided in 3 groups: 54 with low pulse pressure (<40mmHg), 29 with medium pulse pressure (40–49mmHg), 47 with high pulse pressure (>49 mmHg)	Observational comparison study	Pre-treatment vs post-treatment	Knee chest upper cervical	Pulse pressure (-8.9mmHg, p<0.01) in patients with hypertension	Lack of randomization, not a clinical trial

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Table S1 ***(continued)***. Brief description of research studies investigating the effects of chiropractic therapy on hypertension

Plaugher et al 2002[97]	Subdivided in 3 groups: 9 undertook chiropractic, 8 a brief massage, 6 untreated. Study duration: 2 months	comparison trial with 3 parallel groups. Duration: 2 months	Chiropractic group vs brief massage/untreated groups	Gonstead technique	BP decreased in all 3 groups (largest change in control group)	Small cohort
Roffers, Huber et al 2011[99]	331 subjects subdivided in control (108), sham adjustment (117), treatment (106)	Randomized control trial. Duration: 1 treatment	Treatment vs control/placebo	Specific thoracic (T5-T1) chiropractic treatment	Systolic and diastolic BP decreased significantly ($p<0.0001$) in the treatment group. No significant changes in the placebo and control groups	The authors did not collect hypertensive medication history and current usage. The trial was not double-blind. Anxiety might have increased the systolic and diastolic scores before treatment
Roffers, Stiles et al 2011[100]	331 subjects subdivided in control (108), sham adjustment (117), treatment (106)	Randomized control trial. Duration: 1 treatment	Treatment vs control/placebo	Cervical (C3 to occiput C0) chiropractic adjustment	Systolic and diastolic BP decreased significantly ($p<0.0001$) in the treatment group. No significant changes in the placebo and control groups	The authors did not collect hypertensive medication history and current usage. The trial was not double-blind. Anxiety might have increased the systolic and diastolic scores before treatment
Scott et al 2007[105]	20 healthy chiropractic students subdivided in chiropractic adjustment (10), control group(10)	Randomized control trial. Duration: 1 treatment	Treatment vs control	Cervical HVLA	A single cervical adjustment had no effect on systolic or diastolic BP	No hypertensive patients, small cohort
Goertz et al 2016[107]	51 participants with prehypertension or stage 1 hypertension. Treatment group (24), control group (27)	Randomized placebo-controlled clinical trial. Duration: 6 weeks	Treatment vs control	Toggle recoil upper cervical chiropractic	Sham group: systolic BP (-4.2 mmHg), diastolic BP (-1.6 mmHg). Treatment group: systolic BP (0.6 mmHg); diastolic BP (0.7 mmHg). The difference was not statistically significant. No serious adverse events noted	Patients in treatment group treated with antihypertensive medications were not washed out. The sham procedure was not validated for BP studies
Goertz et al 2002[108]	140 subjects with high to normal BP or stage I hypertension subdivided in diet group (69) and chiropractic group (71)	Randomized double-blind controlled trial. Duration: 4 weeks	Chiropractic treatment vs diet treatment	High velocity, short-lever impulse/force applied directly to a joint space	Systolic/diastolic BP average decrease in control group (-4.9/-5.6 mmHg). Systolic/diastolic BP decrease in treated group (-3.5/-4.0 mmHg). No statistically significant changes among groups	Lack of a no treatment control group
Holt et al 2010[109]	70 patients subdivided in treated (35) and control (35) groups	Randomized controlled clinical trial. Duration: 1 treatment	Treatment vs control	Diversified	Systolic blood pressure (-3.9 mmHg, $p=0.002$)	Average changes in blood pressure were not clinically significant

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Table S1 ***(continued)*****.** Brief description of research studies investigating the effects of chiropractic therapy on hypertension

McKnight et al 1988[28]	75 students undergoing routine chiropractic care (53 treated, 22 control group)	Nonrandomized controlled clinical trial. Duration: 1 treatment	Treatment vs control	Cervical adjustment via Gonstead method	Systolic BP (-2.8 mmHg, p<0.01), diastolic BP (-2.6 mmHg, p<0.01) were statistically significantly lower than the controls	Average changes in blood pressure not clinically significant
McMasters et al 2013[29]	24 prehypertensive or hypertensive stage 1, with or without medication	Nonrandomized. Duration: 23 visits	Pre-treatment vs post-treatment	Adjustments from a full spine exam	Average systolic/diastolic BPs (no statistically significant pre/post differences for pre-hypertensive patients, p>0.05). Average systolic BP (-12.8 mmHg, p=0.009), average diastolic BP (-7.6, p=0.0012) for stage 1 hypertensive patients	The patients were not randomized. No control group. High dropout rate. Lack of accounting of confounding determinants of hypertension (diet, exercise)
Schwartzbauer et al 1997[104]	21 male university baseball players aged 19-23 (9 treated, 12 controls)	Longitudinal study with control group. Duration: 14 weeks	Treatment vs control	Upper cervical	No statistically significant differences recorded for blood pressure in controls or treated subjects	Small sample size
Morgan et al 1985[110]	29 randomly selected subjects	Randomized placebo-controlled trial. Duration 18 weeks	Treatment vs control	Osteopathic spinal manipulation, occipito-atlantal and thoracolumbar	No significant difference in the BP after manipulation	Small sample size
Win et al 2015[111]	10 asymptomatic normotensive volunteers + 10 normotensive patients with acute neck pain	Randomized controlled, cross-over. Duration: 1 treatment	Pre-treatment vs post-treatment for both groups	Upper or lower cervical, using high velocity, low amplitude	Systolic BP (-11 mmHg, p<0.05) in asymptomatic normotensive volunteers. Systolic BP (-10 mmHg, p<0.05) in normotensive patients with acute neck pain	Small sample size. No control or sham group. Lack of control over variables (diet, exercise)
Nansel et al 1991[112]	24 healthy, asymptomatic, nonsmoking males (12 treated, 12 controls)	Nonrandomized. Duration: 1 treatment	Treatment vs control	Unilateral lower cervical spinal adjustment	No significant differences between adjusted and non-treated subjects in blood pressure	Small sample size, non-hypertensive subjects
Welch et al 2008[62]	40 patients of 21-55 years old, non-hypertensive, no history of heart disease	Randomized trial. Duration: 1 treatment	Pre-treatment vs post-treatment	Diversified cervical segment adjustment or a diversified thoracic segment adjustment	Diastolic BP (-5.6 mmHg, p=0.038) only after cervical adjustments. No significant reductions for thoracic adjustments	Non-hypertensive patients
Wickes 1980[115]	20 normotensive individuals	Double blind. Duration: 1 treatment	Pre-treatment vs post-treatment	Thoracolumbar spinal manipulation	Systolic BP (+4.0 mmHg) 5 minutes post-manipulation	Non-hypertensive patients
Yates et al 1988[23]	21 hypertensive patients (7 treatment, 7 placebo, 7 no treatment)	Randomized placebo-controlled trial. Duration: 1 treatment	Treatment vs placebo/control	Adjusting instrument to thoracic spine (Activator)	Systolic and diastolic blood pressure decreased significantly in the active treatment condition	Small sample size
Younes et al 2017[116]	17 patients with acute back pain (10 treatment, 7 placebo)	Randomized placebo-controlled trial. Duration: 1 week	Treatment vs placebo	Osteopathic spinal manipulation therapy	No significant differences in the blood pressure	Small sample size, non-hypertensive patients

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Table S1 ***(continued)*****.** Brief description of research studies investigating the effects of chiropractic therapy on hypertension

Ward et al 2013[117]	36 healthy chiropractic college students with less than 32% body fat	3-arm randomized single-blind controlled trial. Duration: 1 treatment	Treatment vs placebo/control	Anterior thoracic manipulation of T1-4	No statistically significant or clinically relevant difference was shown amongst any between-group or within-group cardiovascular dependent variables	Non-hypertensive patients
Ward et al 2015[118]	50 hypertensive patients	Single blind, controlled trial. Duration: 1 treatment	Treatment vs control	Upper thoracic spinal manipulative therapy	Short-term cardiovascular physiology is not affected by upper thoracic spine SMT in hypertensive individuals to a clinically relevant level	Small sample size, the researchers did not include in the exclusion criteria, severe cardiovascular conditions or non-cardiovascular medications that could impact the cardiovascular system
Watanabe et al 2007[119]	11 young healthy adults	Pre/post test comparison. Duration: 1 treatment	Pre-treatment vs post-treatment	Mechanically stimulate cervical manipulation	Significant reductions in BP after application of the mechanical stimulus in the supine posture ($p<0.05$). The reduction peaked at 20 seconds post-stimulation.	Non-hypertensive subjects, small sample size
Dimmick et al 2006[120]	70 Patients (35 treatment, 35 control)	Nonrandomized, matched pair, controlled clinical trial	Treatment vs control	McTimoney technique of chiropractic manipulation	No significant difference between controls and treatment group	Possible selection bias, lack of blinding