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Original Article

P53/P21 Expression Increment as Predisposing Factor for Cancer Development in Hypertensive Patients in Al-Diwaniyah Province, Iraq

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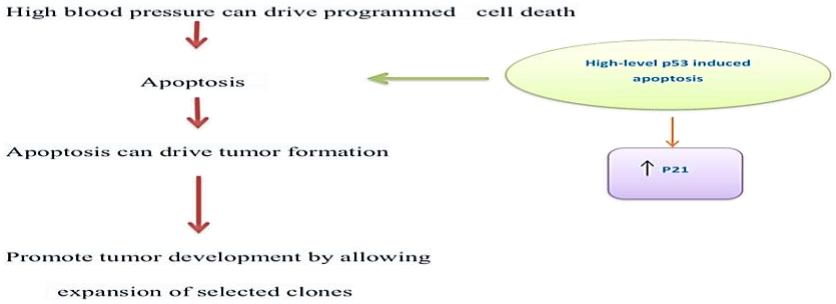
ABSTRACT

Hypertension has been linked to a higher risk of getting some malignancies and a higher cancer-related mortality rate. Furthermore, many anticancer medicines have been linked to developing new high blood pressure or deteriorating previously well-controlled hypertension. The P53 tumor antigen is a mutation-hosting antigen. It is also one of the human tumors' most common genetic changes. Tumor growth is thought to be produced by several stages of genetic damage, which can lead to a breakdown in cell cycle regulatory systems. The objective of this study was to investigate the relationship between high blood pressure and cancer development markers represented by p53, the guardian of the genome, protein expression and its downstream regulator, p21. 20 hypertensive patients (46-70 years of age) were included in this study. Blood samples were collected from two study groups. ELISA Technique was used to detect the protein levels of P53 and P21. The data presented in this study indicate the effect of high blood pressure on cell cycle progression and suggest that programmed cell death is triggered by hypertension, which was reflected by the high expression of P53 and its downstream regulator p21. It is suggested by the data that high blood pressure could be considered a driving force in tumor development through indirect stimulation of cell proliferation to compensate the cell loss by apoptosis which can also drive the development of tumor cells.

GRAPHICAL ABSTRACT



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Introduction

Hypertension is a common chronic age-related illness that often has devastating cardiovascular and kidney effects. Blood pressure is often measured in conjunction with other cardiovascular risk factors. High blood pressure is diagnosed through automated blood pressure monitoring systems. Primary or secondary renal failure to eliminate salt at normal blood pressure is the pathophysiology of essential hypertension. The central nervous system, endocrine variables, significant arteries, and microcirculation are all involved in the condition [1].

Because the first signs of the disease are often evident before a sustained increase in blood pressure, hypertension cannot be characterized simply by blood pressure thresholds. Deteriorations are highly linked to functional and structural cardiac and vascular problems, affecting the heart, kidneys, brain, vasculature, and other organs, increasing morbidity and death [2].

Hypertension is caused by several factors that might be classified as induced causes, such as heredity [3], psychological and social factors [4], high salt intake [5], overweight [6], age [7], hardening of arteries & blood pressure [5], etc. Other causes known as primary causes such as congenital narrowing of the aorta [8], renal defects leading to hypertension [5], inflammation of the arteries walls [9]. In addition, many additional causes may also participate such as aldosteronism, high catecholamine levels, medications and nutrition, Cushing's syndrome and many other factors [10].

Although blood pressure of less than 120/80 was once considered "ideal," it is now considered "normal." Individuals with an untreated systolic blood pressure of 120 to 139 or diastolic blood pressure of 80 to 89 mm Hg are classified as "pre-hypertensive." Stage 1 was the previous classification [4, 11].

Cancer and cardiovascular illnesses are the leading causes of death in developed countries. Body composition, type 2 diabetes, dyslipidemia, and blood pressure are all critical risk factors for cardiovascular disease [12]. According to new evidence, the p53 protein appears to play a role in metabolism. It is found in cell nuclei throughout the body, binding directly with DNA. DNA damage from exposure to chemicals, ultraviolet rays from sun exposure or radiation, p53 protein role following DNA damage is fundamental for the cell. The damaged DNA will be repaired or the injured cell will self-destruct (Undergo apoptosis). If DNA damage can be fixed, this protein blocks the cell from splitting and signals apoptosis if the DNA cannot be repaired. [13].

P53 contributes to cancer prevention by preventing mutant or damaged DNA cell proliferation [14]. The tumor suppressor P53 production is rolled by a gene known as TP53 [15]. P53 expression in adipose tissue has been suggested to be linked to insulin resistance and age-related cardiovascular diseases [16, 17]. P21 induction, a cyclin-dependent kinase inhibitor required for cell cycle progression, is required to suppress growth by p53 in many cell types [18].

P53 proteins that fail to transactivate p21 may result in uncontrolled proliferation and aged-regulated diseases, especially with high p53 expression in adipose tissues [19].

In this study, the correlation between high blood pressure in hypertensive patients and cancer development will be investigated looking at the protein level of p53 and its downstream regulator, p21.

Materials and Method

Samples

A total of 20 hypertensive patients (46-70 years of age) were included in this study. They were admitted to Al-Diwaniyah teaching hospital, compared with 20 non-hypertensive cases. The blood pressure was measured for both hypertensive and non-hypertensive patients (where a level less than 120/80 mm Hg was recorded). Blood samples were collected from two study groups. ELISA Techniques (Abcam P53 human ELISA kit ab46067) and (Abcam P21 human ELISA Kit ab214658) were applied to estimate P53 and P21 levels, respectively, as well as apparently healthy.

Statistical analysis

The values were given as mean ± SE, and the data were analyzed using the ANOVA test with the slightest significant differences (LSD) at a significant level of P<0.05 by using Graph Pad prism 6.0.

Results and Discussion

Serum P53 expression was detected in samples collected from hypertensive patients compared to the expression levels in non-hypertensive cases. The data showed a significant increase in P53 expression in hypertensive patients (~6-fold) compared to non-hypertensive cases (P≤0.05).

No significant changes in P53 expression were noticed between patients under different anti-hypertensive treatment lines (P≤0.05) (Figure 1).

High blood pressure can lead to programmed cell death (apoptosis) [20]. Apoptosis can support tumor growth by encouraging cell proliferation to compensate for cell loss during treatment and restore tissue homeostasis [21-23].

In hypertension, apoptosis has been shown to both improved and diminished in various tissues, including blood vessels. Inflammation, which can be mild, is supposed to play a role in initiating fibrosis, cardiovascular disease, and high blood pressure. Vascular fibrosis is a type of extracellular matrix reshaping in hypertension that involves the accumulation of fibronectin, collagen, and other components in the arterial wall [24, 25]. It was also suggested that extended high blood pressure with greater target organ involvement was associated with increased inflammatory and apoptotic activation in these hypertensive patients [26-30].

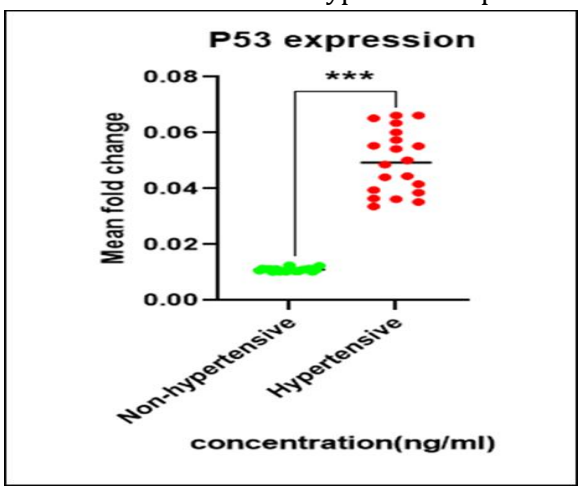

Figure 1: P53 protein expression in Hypertensive and none hypertensive cases

Serum P21 expression was detected in samples collected from hypertensive patients compared to the expression levels in non-hypertensive cases. The data showed a significant increase in P21 expression in hypertensive patients (~4-fold) compared to non-hypertensive cases (P≤0.05).

No significant changes in P21 expression were noticed between patients under different anti-hypertensive therapies (P≤0.05) (Figure 2). The p53 tumor suppressor gene has been demonstrated to up-regulate p21 expression in vitro in response to DNA-damaging chemicals [31-33].

Furthermore, p21 is a direct target of the tumor suppressor p53, and it induces p53-dependent cell cycle arrest in the presence of DNA damage. The method by which p53 controls cell proliferation was unknown until p21 was discovered. The data support what was previously mentioned that p53's activity is mediated by its downstream target genes [34-36].

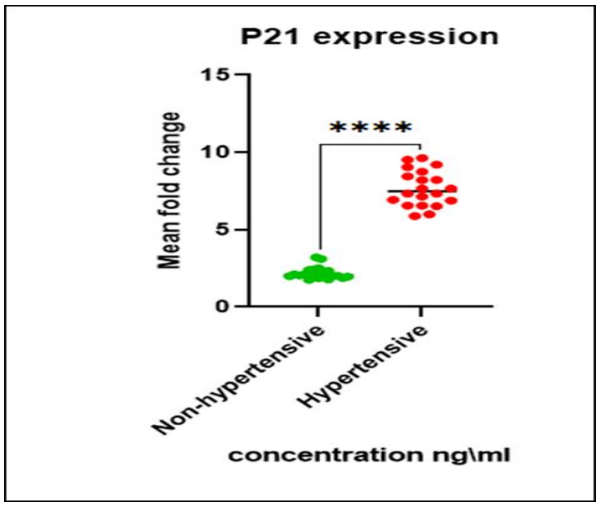

Figure 2: P21 protein expression in Hypertensive and none hypertensive cases

There were no significant differences (P≤0.05) in the data obtained in (age range, gender, occupation, family history of cancer, family history of hypertension, treatment line of hypertension, and usage of other medication) in the expression of P53 and P21 obtained from blood sample analysis of the studied cases. (Figure 3 and 4). The data showed disagreement with Zhang and his colleagues (1994). Who They investigated the effect of carcinogens cigarette smoking and occupations on some carcinogens in the body which might induce TP53 mutations and elaborate in on the development of bladder carcinogenesis [37]. It's It is, otherwise, agreed with Dergham and his colleagues (1997). who They showed the absence of any relation relationship between a family history of cancer and survival in relation to concerning p21 expression in the studied cases [38].

While for age and gender relationship to p53 expression, the current study data came in agreement with Tsai and his colleagues (2005), who suggested an absence of any relationship, according to their data, between p53 and age and gender in the studied cases [39].

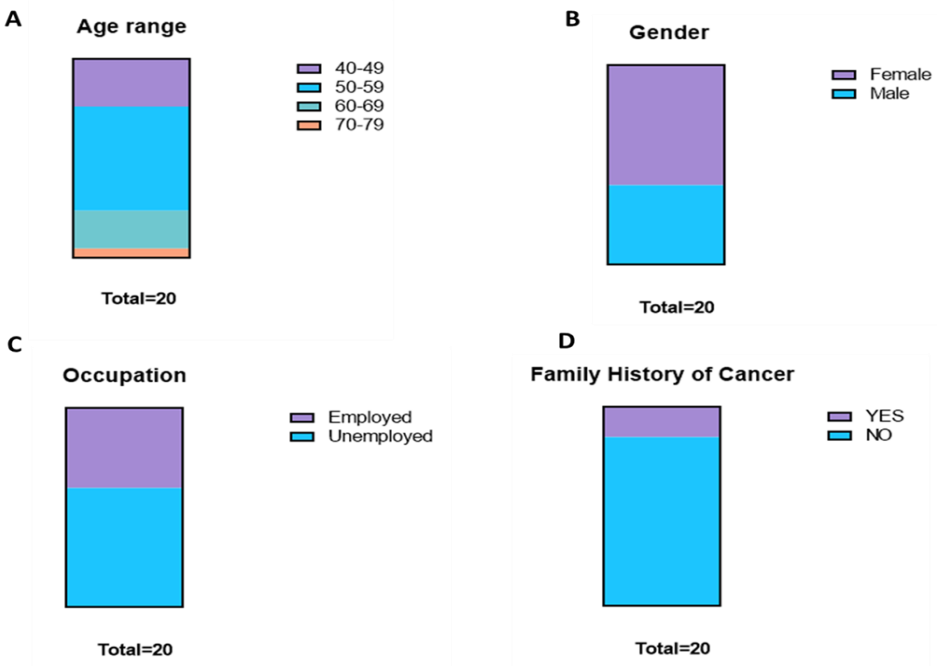

Figure 3: Patients information analysis: (A) Age, (B) Gender, (C) Occupation, (D) Family history of cancer, (E) Family history of hypertension, (F)Treatment line of hypertension, (G)other medications

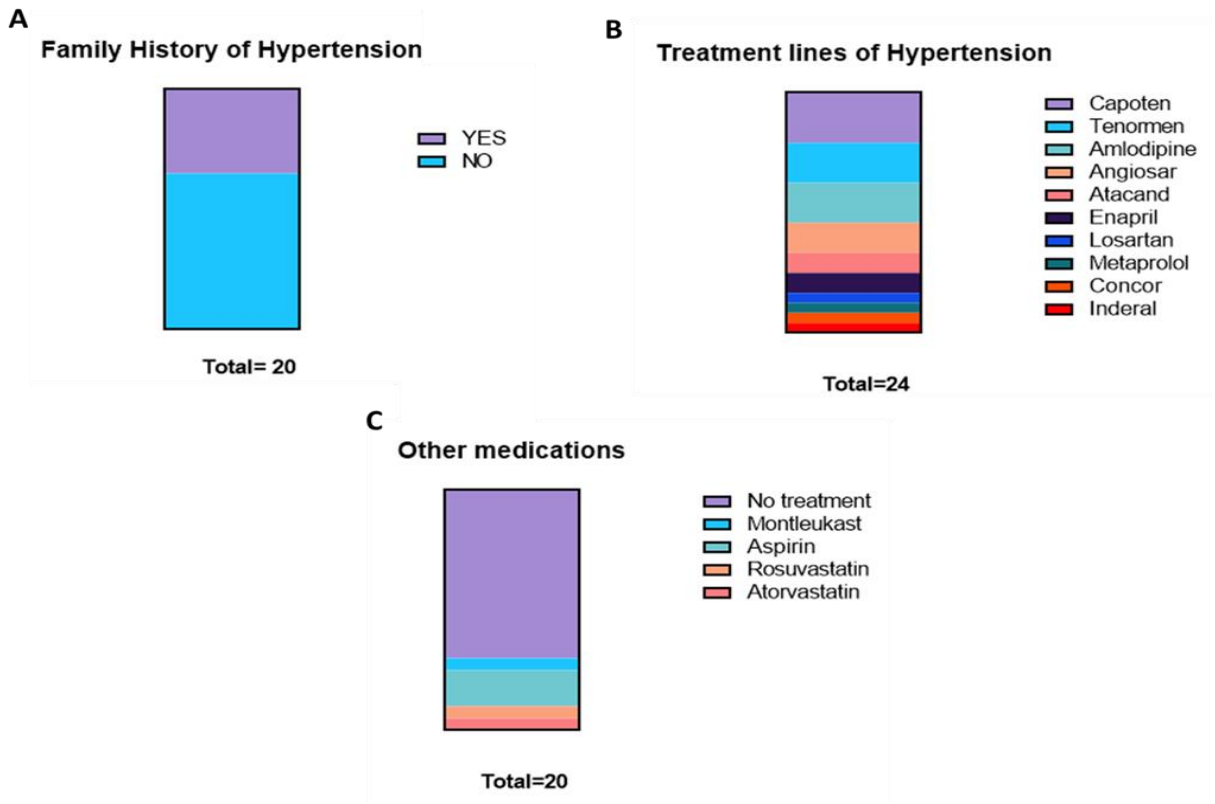

Figure 4: Patients information analysis: (A) Family history of hypertension, (B)Treatment line of hypertension, (C)other medications

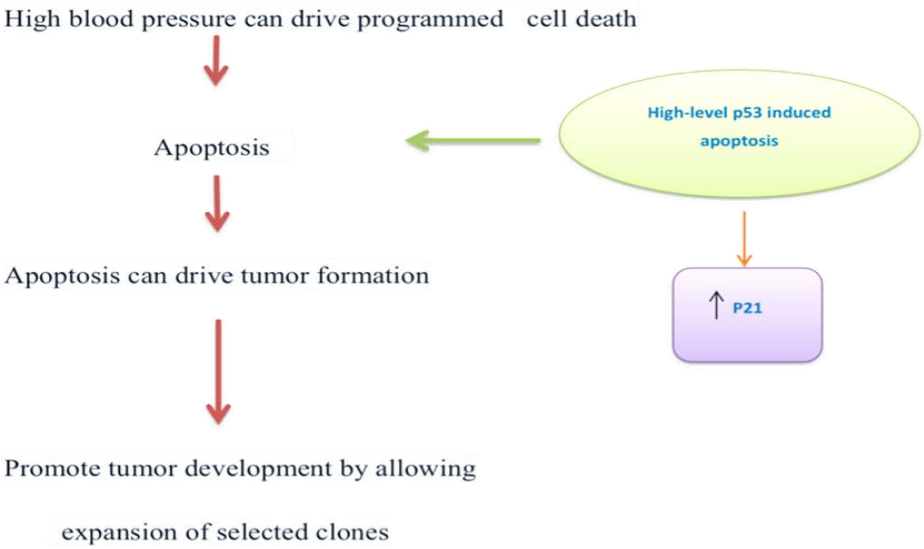

Figure 5: Schematic explanation of the relationship between p53, p21 and cancer development

Conclusion

The data presented in this study indicate the effect of high blood pressure on cell cycle progression and they suggest that programmed cell death is triggered by hypertension which was reflected by the high expression of P53 and its downstream regulator P21. It is suggested by The data suggest that high blood pressure could be considered as a driving force in tumor development through indirect stimulation of cell proliferation to compensate for the cell loss by apoptosis which can also drive the development of tumor cells also

(Figure 5). Further investigations on the expression of TNF-α in addition to tumor suppressor genes BRCA1 and BRCA2 to correlate with the possibility of considering hypertension as a predisposing factor for cancer development in hypertensive patients.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

There are no conflicts of interest in this study.

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