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The Use Of The Parr Function For Understanding The Reactivity Of The Carbenes With β -Himachalene

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Abstract: Cyclopropanes are molecules of great importance since they are present in several biologically active molecules in addition to being powerful intermediates in the synthesis of complex molecules. During this work, we have studied the regio-selectivity of the [1+2] cycloaddition reactions of the carbenes and β -himachalene by the D.F.T method at the level of the basis 6-31 (d), Using a new descriptor of the regio-selectivity concerns the function (office) of Parr. We notice according to this study that the attack of a mole of carbenes is preferentially realized at the level of the C6=C7 connection of β -himachalene in both possibilities of carbenes (nucleophile or electrophile). We also notice that the interaction between orbital borders of reactives (β -himachalene-carbenes) is realized in a facial way. The differences of electrophile $\Delta\omega$ between carbenes {CH(CH₃), :CCl(Ph), :CH(Ph), :CCl(CH₃), :CHF, :CF(Ph), :CF(Cl), :CF₂, :C(Ph)₂, :CH₂, :CHCl, :CCl₂, et :C(Br)₂} and β -himachalene) vary from 0.162eV to 3.408 eV. This shows that all studied reactions have a polar character, unlike reactions using alkoxy-carbenes and silane-carbene {CCl(OCH₃), CF(OCH₃), :C(OCH₃)₂, :C(OH)₂ and :CH(SiH₃). } that have a non-polar character because $\Delta\omega$ is less than 1 ($\Delta\omega < 1$).

Keywords: cycloaddition [1+2], D.F.T, carbenes, nucleophilic power, electrophilic power, polar character, regioselectivity

Introduction

Carbenes have been defined as neutral species with divalent carbon with only six electrons of valence. They have long been considered to be very reactive and difficult to isolate transient species (Figure 1). These compounds are highly reactive, usually known to be unstable and have a very limited lifespan [1-3]. For example, dimethyl carbene [4-5] and dichlorocarbene [6] have, respectively, a half-life of the order of nanosecond and microsecond while dimethoxycarbene has a half-life of 2 milliseconds [7]. This difference in the reactivity of dialkoxycarbenes is largely due to the interaction between n-oxygen electrons and the carbon orbital of carbene, increasing the energy of the $p\pi'$ carbene molecular orbital and ΔE value($p\pi' - \sigma'$). (Figure 1). Thus, these interactions thus give dialkoxycarbenes a nucleophilic character [8].

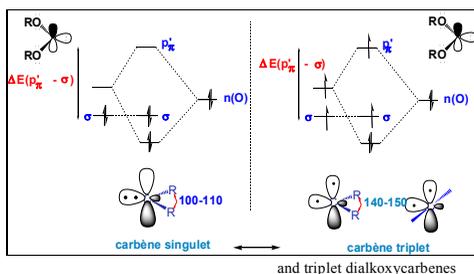


Figure 1: molecular orbital borders of a singlet

Computational methods

The equilibrium geometries have been optimized at the calculation level B3LYP/6-31G(d) [9-11], using the Gaussian 09 [12], program that uses the Berny algorithm [13]. The transition states, corresponding to the two modes of alpha and beta epoxidation, were located at B3LYP/6-31G(d). Their existence has been confirmed by the presence of one and only imaginary frequency in the Hessian matrix. The maximum transfer of charges ΔN_{\max} that will allow us to define the electrophilic power of a system defined so that: $\Delta N_{\max} = -\frac{\mu}{\eta}$. The global nucleophilicity index ω is defined by the expression [14] $\omega = \frac{\mu^2}{2\eta}$ with μ the electronic chemical potential and electronic hardness $\eta = (E_{\text{LUMO}} - E_{\text{HOMO}})$ [15].

Domingo et al. [16] have proposed that for simple molecules if a molecule is weakly electrophilic, then it is systematically strongly nucleophilic: So, to high nucleophilicity values should correspond low values of ionization potentials and vice versa. Using the energies (HOMO) obtained by the Kohn-Sham method [17] the empirical (relative) nucleophilicity (N) index has been defined as follows [18]: $N = (E_{\text{HOMO}(Nu)} - E_{\text{HOMO}(TCE)})$.

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Nucleophilic been has traced to tetra cyano ethylene (TCE) because TCE since TCE has the lowest HOMO energy value in the organic molecules series. The local electrophilic index and the local nucleophilic index were evaluated using the following expressions [19-20]: $\omega_k = \omega.P^+$ and $N_k = N.P^-$ such as P^+ and P^- are the functions of electrophilic and nucleophilic Parr respectively [21-22] are obtained from the Mulliken atomic density analysis of the anion and the neutral molecule cation.

Results and discussion

In a simple way, the fundamental state of a carbene can be determined by comparing the values of $\Delta E(p\pi^*-\sigma^*)$ to electronic and steric repulsion energies. In the event that the value of $\Delta E(p\pi^*-\sigma^*)$ to the orbital $p\pi^*$ to obtain the triplet state becomes more important than the electronic and steric repulsion energies related to the singlet state. A singular fundamental state is then observed. It has been suggested in the past that an existing carbene in the fundamental state singlet had a value of $\Delta E(p\pi^*-\sigma^*)$ greater than 2 eV (46 kcal/mol) while a triplet carbene had a value of $\Delta E(pp-\sigma^*)$ less than 1.5 eV (35 kcal/mol). [23]. These trends have been confirmed by Mendez in a theoretical study on the electronic structure of a variety of carbenes. [24]. The latter has established that the value of ΔEST (by convention, a negative value of ΔEST implies a singlet state lower in energy than the triplet state). In the case of dimethoxycarbene, an ΔEST of -53.0 Kcal/mol was calculated (Table 1). In 2011 Kassae has reported similar TSE values of -57.0 and -55.0 Kcal/mol [25].

Table 1: ΔE_{ST} values calculated for the different carbenes

	Carbene	ΔE_{ST} (Kcal/mol)
1	CH(SiH3)	23,3
2	CH2	13,7
3	CH(CH3)	7,9
4	CCl(Ph)	-4,6
5	CHCl	-2,2
6	CH(Ph)	7,1
7	CCl(CH3)	-4,9
8	CHF	-12,1
9	CF(Ph)	-13,3
10	CCl2	-16,6
11	CF(Cl)	-33,4
12	CCl(OCH3)	-36,0
13	3)	-51,8
14	CF(OCH3)	-52,1
15)	-53,0
16	CF2	-54,5
	C(OCH3) 2	
	C(OH)2	

Prediction of relative reactivity of reagents and polarity of cycloaddition reactions

The polar character of AD reactions can be obtained from the difference in the overall electrophiles of the reagents. This difference was used to determine the polar character of this type of reaction. Indeed, recent studies of AD reactions have shown that DFT-derived reactivity indices are an effective tool for establishing the polar/non-polar character of cycloaddition reactions[26]. The calculated values of the overall reactivity indices, namely the electronic chemical potential μ , global hardness η , global electrophilic ω , global nucleophilicity N and the overall maximum load transfer ΔN_{max} for reagents are given in Table 2.

Table 2: HOMO/LUMO energies, electronic chemical potential μ , global hardness η , global electrophilicity ω , global nucleophilicity N and maximum overall load transfer/ N_{max} of carbenes 1-18 and β -himachalene.

Reactifs	carbene	HOMO	LUMO	μ	η	ω	N	ΔN_{max}
1	CH(SiH ₃)	-6,179	-1,006	-3,592	5,173	1,247	3,353	0,694
2	CH ₂	-6,625	-3,303	-4,964	3,322	3,708	2,907	1,494
3	CH(CH ₃)	-5,695	-2,076	-3,885	3,619	2,085	3,837	1,073
4	CCl(Ph)	-5,747	-2,925	-4,336	2,822	3,331	3,785	1,536
5	CHCl	-6,708	-3,292	-5	3,416	3,659	2,824	1,463
6	CH(Ph)	-5,181	-2,666	-3,923	2,515	3,06	4,351	1,559
7	CCl(CH ₃)	-6,206	-2,557	-4,381	3,649	2,63	3,326	1,2
8	CHF	-6,623	-2,557	-4,59	4,066	2,59	2,909	1,128
9	CF(Ph)	-5,774	-2,457	-4,115	3,317	2,553	3,758	1,24
10	CCl ₂	-7,357	-3,551	-5,454	3,806	3,907	2,175	1,433
11	CF(Cl)	-7,771	-2,998	-5,384	4,773	3,037	1,761	1,128
12	CCl(OCH ₃)	-6,669	-1,496	-4,082	5,173	1,61	2,863	0,789
13	CF(OCH ₃)	-6,775	-0,767	-3,771	6,008	1,183	2,757	0,627
14	CF ₂	-8,088	-2,111	-5,099	5,977	2,175	1,444	0,853
15	C(OCH ₃) ₂	-5,806	-0,008	-2,907	5,798	0,728	3,726	0,501
16	C(OH) ₂	-6,443	-0,137	-3,29	6,306	0,858	3,089	0,521
17	C(Br) ₂	-7,061	-3,6	-5,33	3,461	4,104	2,471	1,54
18	C(Ph) ₂	-5,533	-3,045	-4,289	2,488	3,696	3,999	1,723
19	β -himachalene	-5,692	----	-2,499	6,488	0,696	3,999	0,385

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In the case of the reaction (1) between β -himachalene and CH(SiH₃) carbenes, the electronic chemical potential of β -himachalene ($\mu = -2.499$ u.a) is higher than that of CH(SiH₃) carbenes ($\mu = -3.592$ u.a); this indicates that the transfer of electrons will take place from β -himachalene to the CH(SiH₃) carbenes. On the other hand, the overall electrophilic index of β -himachalene ($\omega = 0.696$ eV) is lower than that of carbeneC(Ph)₂ ($\omega=1,247$ eV) and therefore CH(SiH₃) carbenes behave like an electrophilic, while β -himachalene behaves like a nucleophile. It is noted that the overall nucleophilicity indices also show that carbeneCH(SiH₃)($N=3.353$ eV) is less nucleophilic than β -himachalene ($N=3.427$ eV). In addition, ΔN_{max} , which represents the maximum load ratio that can be acquired by a system of its environment, is maximum for CH(SiH₃)(0,694) and minimum for β -himachalene (0,385).

For the reaction (2) between β -himachalene and CH₂ carbenes, the electronic chemical potential of β -himachalene ($\mu = -2.499$ u.a) is higher than that of CH₂ carbenes ($\mu = -4.964$ u.a); this indicates that the transfer of electrons will take place from β -himachalene to CH₂ carbenes. On the other hand, the overall electrophilic index of β -himachalene ($\omega = 0.696$ eV) is lower than that of carbeneCH₂($\omega= 3.708$ eV) and therefore carbene CH₂ behaves like an electrophilic, while β -himachalene behaves like a nucleophile. It is noted that the overall nucleophilicity indices also show that CH₂ ($N = 2.907$ eV) is less nucleophilic than β -himachalene ($N = 3.427$ eV). In addition, ΔN_{max} , which represents the maximum load ratio that can be acquired by a system of its environment, is maximum for CH(SiH₃)(0,694) and minimum for β -himachalene (0,385).

It is noted that the same remarks are observed during the reaction of β -himachalene with other carbenes {CH(CH₃), CCl(Ph), CHCl, CH(Ph), CCl(CH₃), CHF, CF(Ph), CCl₂, CF(Cl), CCl(OCH₃), CF(OCH₃), CF₂, C(OCH₃)₂, C(OH)₂, C(Br)₂ and C(Ph)₂}.

In order to show the donor (nucleophilic) or acceptor (electrophilic) character of the two reagents and the polar character of the reactions, we calculated the HOMO/LUMO energy gaps of the reagents and the differences in electrophilicity (Table 3).

Table 3: Difference between the two possible combinations HOMO/LUMO and $\Delta\omega$.

Reactions	Carbenes	A	B	$\Delta\omega(\text{eV})$
1	:CH(SiH3)	6,872	4,6859	0,551
2	:CH2	7,318	2,388	3,012
3	:CH(CH3)	6,388	3,615	1,389
4	:CCl(Ph)	6,44	2,766	2,635
5	:CHCl	7,401	2,399	2,963
6	:CH(Ph)	5,874	3,025	2,364
7	:CCl(CH3)	6,899	3,134	1,934
8	:CHF	7,316	3,134	1,894
9	:CF(Ph)	6,467	3,234	1,857
10	:CCl2	8,05	2,14	3,211
11	:CF(Cl)	8,464	2,693	2,341
12	:CCl(OCH3)	7,362	4,195	0,914
13	:CF(OCH3)	7,468	4,924	0,487
14	:CF2	8,781	3,58	1,479
15	:C(OCH3)2	6,499	5,683	0,032
16	:C(OH)2	7,136	5,554	0,162
17	:C(Br)2	7,754	2,091	3,408
18	:C(Ph)2	6,226	2,646	3

**A:

Table 2 also shows that the $|E_{\text{HOMO}}^{\beta\text{-himachalene}} - E_{\text{LUMO}}^{\text{carbene}}|$ are lower than the $|E_{\text{HOMO}}^{\text{Carbene}} - E_{\text{LUMO}}^{\beta\text{-Himachalene}}|$ differences in the 18 reactions.

In conclusion, for the 18 reactions studied, carbenes behave like electrophiles (electron acceptors) and β -himachalenebe has like nucleophiles (electron donors).

Table 2 also shows that electrophilic differences, varies from 0.162 eV to 3.408 eV; showing that all reactions studied have a polar character except reactions where alkoxy-carbenes and silane-carbene are used $\{:\text{CCl}(\text{OCH}_3), :\text{CF}(\text{OCH}_3), :\text{C}(\text{OCH}_3)_2, :\text{C}(\text{OH})_2 \text{ and } :\text{CH}(\text{SiH}_3)\}$ have a non-polar character because $\Delta\omega$ is less than 1 ($\Delta\omega < 1$) [27].

According to the differences in terms of $|E_{\text{HOMO}}^{\beta\text{-himachalene}} - E_{\text{LUMO}}^{\text{carbene}}|$ and $|E_{\text{HOMO}}^{\text{Carbene}} - E_{\text{LUMO}}^{\beta\text{-Himachalene}}|$ and $\Delta\omega$ mentions in Table 2 it can be concluded that:

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➤ The values of $\Delta\omega$ for reactions 13-15 (experimental data not available) are lower than those of previous reactions 1-12 (experimental data available). Therefore, reactions 13-15 have been predicted to be more kinetically disadvantaged compared to reactions 1-12;

➤ The gaps (HOMO/LUMO) for β -himachalene reactions with the following carbenes: $:\text{CH}(\text{SiH}_3)$, $:\text{CCl}(\text{OCH}_3)$, $:\text{CF}(\text{OCH}_3)$, $:\text{C}(\text{OCH}_3)_2$, and $:\text{C}(\text{OH})_2$. are greater than those of the β -himachalene reactions with the following carbenes: $:\text{CH}(\text{CH}_3)$, $:\text{CCl}(\text{Ph})$, $:\text{CH}(\text{Ph})$, $:\text{CCl}(\text{CH}_3)$, $:\text{CHF}$, $:\text{CF}(\text{Ph})$, $:\text{CF}(\text{Cl})$, $:\text{CF}_2$, $:\text{C}(\text{Ph})_2$, $:\text{CH}_2$, $:\text{CHCl}$, $:\text{CCl}_2$, and $:\text{C}(\text{Br})_2$. These results show that the reactions of β -himachalene with the following carbenes: $:\text{CH}(\text{SiH}_3)$, $:\text{CCl}(\text{OCH}_3)$, $:\text{CF}(\text{OCH}_3)$, $:\text{C}(\text{OCH}_3)_2$, and $:\text{C}(\text{OH})_2$. are more kinetically difficult compared to the reactions of β -himachalene with the following carbenes: $:\text{CH}(\text{CH}_3)$, $:\text{CCl}(\text{Ph})$, $:\text{CH}(\text{Ph})$, $:\text{CCl}(\text{CH}_3)$, $:\text{CHF}$, $:\text{CF}(\text{Ph})$, $:\text{CF}(\text{Cl})$, $:\text{CF}_2$, $:\text{C}(\text{Ph})_2$, $:\text{CH}_2$, $:\text{CHCl}$, $:\text{CCl}_2$, and $:\text{C}(\text{Br})_2$ as already predicted with the values of $\Delta\omega$.

Prediction of the region- chemoselectivity of the cycloaddition reactions studied

The best descriptors for studying local reactivity and regioselectivity of a cycloaddition reaction are local electrophilia [28] and local nucleophilia [27]. In a polar cycloaddition reaction between two replacement reagents. The interaction at two most favourable centres will take place between the most electrophilic centre characterized by the highest value of the local electrophilia index ω_k in the electrophilia, and the most nucleophilic center characterized by the highest value of the N_k local nucleophilia index in the nucleophilia. The local electrophilic powers and local nucleophilic power the 18 carbenes and atoms C2, C3, C6 and C7 atoms of β -himachalene calculated using the function of Parr (Spin Atomic Density) are given in Table 4.

Table 4: Local electrophilic and nucleophilic power for the 18 carbenes and β -himachalene obtained by a Parr function calculus (atoms C2, C3, C6 and C7 of β -himachalene).

Carbenes	Reagents	P^+	P^-	ω_k	N_k
1	CH(SiH3)	0,953	0,95	1,188	3,185
2	CH2	1,092	0,989	4,049	2,875
3	CH(CH3)	1,044	0,925	2,176	3,549
4	CCl(Ph)	1,01	0,535	3,364	2,024
5	CHCl	1,014	0,84	3,71	2,372
6	CH(Ph)	1,135	0,545	3,473	2,371
7	CCl(CH3)	0,963	0,783	2,532	2,604
8	CHF	0,983	0,84	2,545	2,443
9	CF(Ph)	0,98	0,533	2,501	2,003
10	CCl2	0,974	0,674	3,805	1,465
11	CF(Cl)	0,914	0,691	2,775	1,216
12	CCl(OCH3)	0,894	0,703	1,439	2,012
13	CF(OCH3)	0,873	0,737	1,032	2,031
14	CF2	0,899	0,769	1,955	1,11
15	C(OCH3)2	0,85	0,723	0,618	2,693
16	C(OH)2	0,916	0,932	0,785	2,878
17	C(Br)2	0,66	0,638	2,708	1,576
18	C(Ph)2	1,087	0,606	4,017	2,423
β - himachalene	C2	0,08	0,14	0,05	0,47
	C3	0,13	0,09	0,09	0,3
	C6	0,27	0,25	0,18	0,85
	C7	0,28	0,27	0,19	0,92

Static evidence of local electrophilia ω_k and N_k local nucleophilia are reliable descriptors for the prediction of the interaction electrophilia-nucleophilia most favoured for the formation of a chemical bond between two atoms. The values of local electrophilia ω_k for carbenes and N_k local nucleophilia for atoms C2, C3, C6 and C7 of β -himachalene, calculated with the function Parr (Spin Atomic Density) are reported in Table 4. The results show that the most favoured interaction will take place between the carbon atom of the carbene (having the highest value of ω_k) and the atoms C6 and C7 of the β -himachalene (having the highest value of N_k). Therefore, the experimentally observed regioselectivity is correctly predicted by the Parr functions.

For carbenics 15 and 16 the electrophilic power decreases, which indicates that carbenicC(OCH₃)₂($\omega = 0.728$ eV) is the least electrophilic system of this series. Therefore, Carbenes 15 and 16 can play the role of a nucleophile, so two approaches can be classified:

Interactions between β -himachalene HOMO and carbenes LUMO Figure 2.

The electrophilic attack of carbenes on β -himachalene takes place on the C6=C7 bond and allows to form cyclopropane, a study shows that the reaction of an equivalent of dichlorocarbene with an equivalent of β -himachalene is highly regio-selective [29], the interaction is between HOMO β -himachalene and LUMO carbene in a facial way (Figure 2).

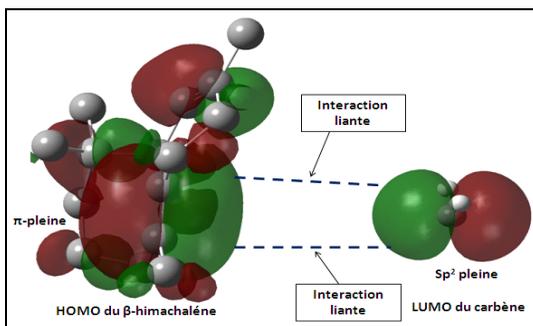


Figure 2: Optimized structures and HOMO densities of β -himachalene and LUMO carbene density calculated by the B3 lyp/6-31 G(d) method.

Interactions between β -himachalene LUMO and carbene HOMO Figure 3.

The nucleophilic attack of the carbene (nucleophilic power of the carbenes is greater than the nucleophilic power of the β -himachalene) takes place at the level of the C6=C7 link because the local electrophilic power of the sites C6 and C7 is at the site of the sites C2 and C3, and the interaction between the Homo orbital of the carbene and LUMO of the β -himachalene and we find that the attack is facial (Figure 3).

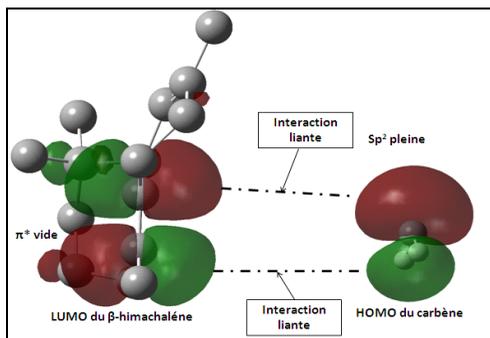


Figure 3: Optimized structures and densities of β -himachalene and HOMO carbene density calculated by the B3 lyp/6-31 G(d) method.

As mentioned above, the interaction between the orbital boundaries of the reagents is done in a facial way, one reagents approach each other the groupings substituted the carbenes rotates out of the formed cyclopropanation to minimize steric congestion.

Conclusion.

The regioselectivities of β -himachalene cycloaddition reactions [1+2] have been studied using the index of local nucleophilicity recently proposed by Domingo, P. Pérez and J. A. Sáez (Parr functions). Our results show that the experimental regioselectivities are correctly reproduced with this empirical index which proves to be more reliable than the net loads. Indeed, the index of local nucleophilicity predicts that the double link C6=C7 is more reactive than the link C2=C3 in both cases where β -himachalene plays the role of an electrophile or a nucleophile.

The difference in electrophilicity between β -himachalene and carbenes makes it possible to classify these cycloaddition reactions into two categories:

Non-polar reactions where the following carbenes are used: $(:CH(SiH_3), :CCl(OCH_3), :CF(OCH_3), C(OCH_3)_2, :C(OH)_2)$.

Polar reactions if the following carbenes are used: $(:CH_2, :CH(CH_3), :CCl(Ph), :CHCl, :CH(Ph), :CCl(CH_3), :CHF, :CF(Ph), :CCl_2, :CF(Cl), :CF_2, :C(Ph)_2)$.

Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper. Also, they declare that this paper or part of it has not been published elsewhere.

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Peculiarities Of The Course Of Chronic Kidney Disease In Various Components Of Metabolic Syndrome

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Abstract: Study of some indicators of metabolism and velocity of ballast filtration in patients with chronic kidney disease.

Key words: chronic kidney disease,metabolism, ballast filtration,abdominal obesity,glucose tolerance

Purpose of work: study of some indicators of metabolism and speed of ball filtration in patients with chronic kidney disease. To estimate the connection between body weight and BFS, 97 patients with chronic chronic kidney disease had increased creatinine content (165 ± 7.83 $\mu\text{mol/l}$) in their blood and, as a comparison group, 95 people with normal creatinine values (85 ± 5.12 $\mu\text{mol/l}$). The average age of the patients was 39 ± 8.7 years. When analyzing the velocity of ballast filtration, it is more expedient to study it by the formula Cockcroft-Gault /1.73 m² (reduced to the normal body surface) than by the usual formula Cockcroft-Gault. Not only does the presence of NVT have a negative effect on the reduction of the spongiform filtration rate, but also its category.

Chronic kidney disease (CAD) is a global medical problem that has become a modern medical and social problem (Andrew S. Levey et al., 2015). This is due to the high prevalence of CAD, as well as the high number of complications of the disease. High disability and mortality rates, as well as significant material costs for the treatment of this category of patients, give high social importance to CAD (Siegmond-Schultze, Nicola. 2014). International statistics indicate that the number of patients with chronic renal failure (CRF) continues to increase progressively in all countries (Almaguer M, et al., 2014; KDIGO, 2009; Ermolenko V.M. et al., 2011).

Chronic kidney disease (CAD) is among the most important diseases of our time in terms of prevalence and socio-

economic damage, such as diabetes mellitus and metabolic syndrome, arterial hypertension, cerebrovascular disease and ischemic heart disease (Smirnov A.V. et al., 2011; War-wick G., et al., 2014; Wissam Saliba et al., 2015). CAD problems are acute in both developed and developing countries (B.T. Bibkov and N.A. Tomilina, 2009; M.Y. Shvetsov et al., 2011).

One of the most important criteria for CAD is the state of ballast filtration speed (BFS). Analysis of publications shows that the forecast for CAD significantly depends on the size of the BFS. In this connection, CAD is divided into five stages [National Kidney Foundation KD., 2002]. At the same time, CDP screening and diagnosis cannot be based only on the calculation of BFS, because this indicator is largely related to other diseases and pathological conditions. Along with BFS, protein excretion, including albuminuria/proteinuria, is also a major focus in the diagnosis and monitoring of CAD. This is due to the fact that they are important indicators of prognosis, as well as the efficacy of CAD treatment.

Materials and methods: In order to estimate the rate of cleavage filtration and creatinine clearance in CAD patients depending on the components of the metabolic syndrome, the following methods were used. Since the purpose of this work was to determine the degree of influence of some basic components of MS on the state of BFS in all patients, the main components of the metabolic syndrome were studied, which were identified on the basis of criteria of the International Diabetes Federation (IDF), adopted in 2005. [IDF, 2005].

At the same time, considering the fact that in severe stages of chronic renal failure (CRF) there are marked metabolic disorders that can to some extent distort the results of the work, this study did not include patients with a pronounced decrease in BFS and terminal CRF (BFS less than 30 ml/min). Patients representing CAD up to and including stage III (BFS up to 30 ml/min) were examined.

The state of glucose tolerance was determined by a standard oral glucose tolerance test (GTT) with the determination of fasting glycemia, as well as 2 hours after the test subject took 75 g of glucose. Glucose level was studied in capillary blood by means of automatic glucoanalyzer "GlucoDr" (South Korea).

WHO's AG classification (WHO, 1999) and the criteria of the Russian Federation FOI experts (second revision, 2004) were used to assess BP. Individuals with levels of Mean arterial pressure ≥ 140 mmHg, and/or Diastolic blood pressure ≥ 90 mmHg were included in the group with AH. The group of patients with AH also included persons with normal Arterial hypertension values, but who took hypotensive drugs within 2 weeks before the examination. Abdominal obesity (AO) was detected in individuals with waist circumference > 94 cm. Hypertriglyceridemia (HTG) was taken to be a blood triglyceride > 1.7 mmol/l.

According to the criteria of metabolic syndrome all patients were divided into 4 groups (Table 1). Each group included persons with or without one of the main components of MS (Impaired glucose tolerance, Arterial hypertension and Pituitary gonadotropin hormones).

Table 1.

Groups	Quantity
Group 1. Glucose intolerance disorder	
Patients without NTG	30
NTG on an empty stomach	30
NTG after 2 hours	31
Group 2. Hypertriglyceridemia	
Patients without NTG	32
Patients with NTG	35
Group 3. Abdominal obesity	
Patients without abdominal obesity	31
Patients with abdominal obesity	27
Group 4. Arterial hypertension	
Patients without arterial hypertension	30
AG 1 st.	29
AG 2 st.	27
AG 3 st.	29

CAD was diagnosed based on KDOQI criteria (2002), in which 5 stages of the disease are distinguished. The following clinical signs of the disease were considered: fatigue, drowsiness, apathy, muscle weakness, polyuria, nicturia, skin and neurological symptoms; albuminuria, proteinuria, hematuria, creatinine, urea, as well as morphological changes and visualization studies. Patients with CAD in all groups received basic treatment, including a diet with protein restriction, means of correcting disturbed parameters of homeostasis, hypotensive drugs, antianemic drugs, etc.

The rate of ball filtration was calculated by the formula MDRD

(Modification of Diet in Renal Disease Study), which allows to take into account this index with its standardization by body surface area. To evaluate the connection between body weight and BFS, 97 patients with CAD were examined, who had an increased creatinine content ($165 \pm 7.83 \text{ } \mu\text{mol/l}$) in their blood and, as a comparison group, 95 people with normal creatinine values ($85 \pm 5.12 \text{ } \mu\text{mol/l}$). The average age of the patients was 39 ± 8.7 years.

The speed of the ball filtering was calculated by two formulas: Cockcroft-Gault formula based on Cockcroft-Gault = $88 \times (140 \text{ years old, years old}) \times \text{body weight, kg} / 72 \times \text{serum creatinine, } \mu\text{mol/}$

l; BFS formula for Cockcroft-Gault)/1.73 m² (reduced to normal body surface).

Body mass and surface area were studied based on the following indicators: Body Mass Index (BMI) in kg/m² calculated by the formula: weight(kg)/rost(m)². According to the BMI index, underweight groups of less than 18.5 BMI; normal weight groups of between 18.6 and 24.9 BMI; overweight groups of between 25 and 29.9 BMI; obesity groups of more than 30 BMI; and surface area of the body (according to Mosteller, 1987).

Results and discussion.

According to the results obtained in

Group 1 (Fig. 1), a link between hyperglycemia and BFS was revealed. In persons without STG, BFS was within normal limits and exceeded similar parameters in groups with hyperglycemia. At the same time, large and statistically significant ($p < 0.05$) differences were revealed in relation to the values of BFS between non BFS and the presence of NTG 2 hours after glucose loading. For example, BFS was 18% lower among individuals with fasting hyperglycemia and 25.5% lower among patients with hyperglycemia after 2 hours than among individuals with normal glycemia.

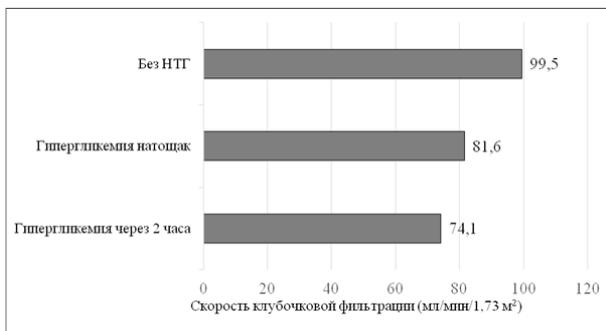


Figure 1: Gobeella filtration rate in group 1 in patients with CAD with NTG

The results indicate that NTG, which is an insulin resistance marker, is associated with the state of barrel-glass filtration. Other studies have also shown that diabetes mellitus is associated with CAD, in particular the reduction of BFS disease [8,10]. It is pointed out that in countries such as the USA, Germany and Japan, the share of diabetic nephropathy in the structure of dialysis service reaches 35-45% [Excerpts from the United States Re-nal Data System 2007 annual data report., 2008].

Taking into account the fact that NTG, as a precursor to type 2 diabetes mellitus and, in some cases, is transformed into this disease, it is necessary to recognize the important role of latent hyperglycemia in the pathogenesis of CDP.

The question arises - what are the prospects for the treatment and primary and secondary prevention of CAD in patients with insulin resistance? Work in this area is not yet sufficient. Perhaps the most interesting is the P study. Fioretto, which is currently the only work based

on a 10-year prospective study [Mark S. MacGregor and Maarten W. Taal., 2011]. In this study it was shown that normalization of carbohydrate metabolism can lead not only to improvement of the functional state of the kidneys, but also to improvement of its morphological state. It should be noted that the reverse development of sclerotic changes of renal balls was achieved only after 10 years of stable normoglycemia.

The main components of MS also include abdominal obesity and hyperlipidemia. In our study (according to IDF criteria, 2005), hyperlipidemia was recorded in the presence of hypertension-lipidemia (HTG). According to the data obtained in groups 2 and 3 (Fig. 2), BFS in patients with AO and GTG was reduced. However, the presence of HTG is more associated with a decrease in BFS. The difference between BFS in patients

with CAD and absence of PEП is 20.9 / min/1.73 m² l/min/1.73 m². The same indicator for patients with AR presence and absence was 15.5 ml/min/1.73 m².

These data indicate that the assessment of renal conditions, treatment and prevention of CAD should take into account and prevent the development of these components of MS.

There are indications that the relationship between Arterial hypertension and renal function is sufficiently large. However, it is also important to keep in mind that the causal relationship between kidney and heart diseases is interrelated. In particular, kidney disease may cause AH, and this in turn may act as a risk factor for kidney disease.

Our study has shown that the degree of AB severity and the condition of BFS are inversely related (Fig. 3).

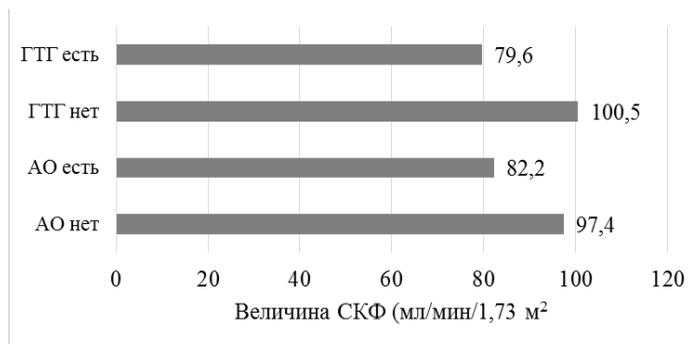


Figure 2: BFS in patients with CAD with hypertriglyceridemia (HTG) and abdominal obesity (AO).

Analysis of the data obtained in group 4 shows that in persons without AH BFS is within normal limits (103.6 ml/min/

1.73 m²). As the degree of AH increases, a decrease in BFS is observed. Thus, at 1 step-ni AH there is a slight decrease in BFS to 94.1 ml/min/1.73 m².

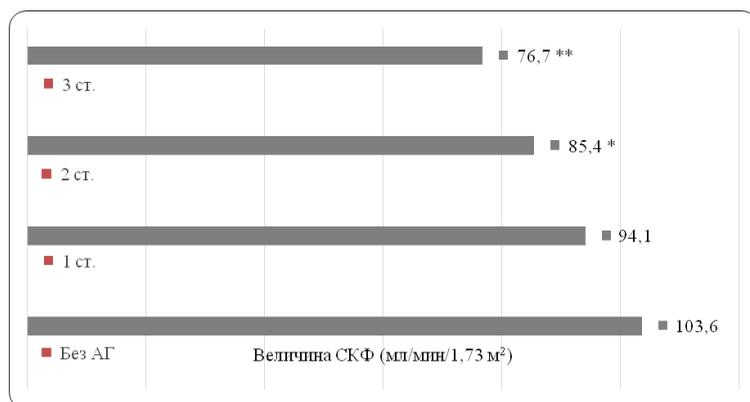


Figure 3: Grooved filtration rate in patients with different AH step-foam.

At the same time, patients with blood pressure levels higher than 160/100 mmHg. BFS decreases to 85.4 ml/min, and at the third degree it reaches 76.7 ml/min/1.73 m², which is almost ^{1/4} lower than at normal blood pressure.

Conclusions:

When analyzing the velocity of ballast filtration, it is more appropriate to study it using the formula Cockcroft-Gault /1.73 m² (reduced to a normal body surface) than the usual form of Cockcroft-Gault.

Not only is the presence of NTG a negative effect on the decrease in the rate of glomerular filtration, but also its category. In the greater step-foam, BFS reduces the disruption of the carboinsular phase of the glycemc curve

(hyperglycemia 2 hours after glucose loading).

Abdominal obesity, hypertriglyceridemia and arterial hypertension are also closely related to the rate of glomerular filtration, which is significantly reduced in the presence of these MS components.

Body weight and surface may serve as markers of the velocity of the barrel-glass filtration. Therefore, the assessment of the state of ballast filtration rate in patients with chronic kidney disease should be carried out taking into account the body weight and surface.

Treatment and prophylactic measures for CAD and, in particular, BFS, should be carried out taking into account the main components of MS.

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Junk Food: Impact On The Eating Habits Of University School Undergraduate In Tepic Mexico

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Abstract: Background: to analyze the relationship between the consumption of junk food and the physical complexion and healthy lives of undergraduate students.

Methods: Design: Descriptive and observational study. Setting: Universidad Vizcayade las Am?ricas, campus Tepic Nayarit Mexico. Participants: volunteers university undergraduates bachelor: 79 of Physiotherapy (BPh), 34 of Nursing (BNu) and 48 of Psychology (BPs). The anthropometric assessment (height, weight, BMI, waist circumference (WC), Hip circumference (HC), and waist-hip ratio (WHR)) was measured using standard methods. Junf food and anthropometrics were analyzed by Pearson Correlation Coefficient.

Results: BNu and BPs were always consuming the most junk food with 68.6% and 67.3%, respectively. Junk food is generally consumed inside of the University and in the street food stall that are around the university. Cookies, hamburgers, pizza, chips, tacos are some junk food most consumed by students. More of 85% of students of three bachelors had overweight. There was a relationship between junk food consumption and anthropometric measurements in all bachelors.

Conclusion: Junk food had impact on anthropometric measurements of students.

Keywords: Junk food, students undergraduate, Vizcaya de las Americas university, anthropometric assessment.

Introduction

Junk food is a name for foods that do not meet people's nutritional needs, i.e., these foods provide minimal amounts of protein, vitamins or minerals, and provide a large amount of calories from carbohydrates or lipids¹⁻². In this group included salty snacks, snacks, flours, treats, bubble gum, pastries, fast food, soft drinks, greaves, ice-cream and fried foods³. Similarly, these foods are commonly sold in educational establishments at all levels (kindergarten, first grade, middle school, high school, university), in stores, supermarkets and in strategic places that are installed outside schools for rapid consumption due to lack of time, and cause a culture to adopt its consumption and low cost on a regular basis. Its frequent consumption can cause overweight and obesity⁴⁻⁶.

Mexico is a country that occupies in the first places of obesity and childhood obesity, this as a result of food factors, in them the daily consumption of junk food as part of people's daily menu. According to the Ministry of Health (SSA), in Mexico around 240 billion pesos are spent annually in the purchase of junk food and 40% of school spending on junk food, so that eight out of ten children consume them⁶. Therefore, there is consensus on the urgent need to seek critical points to address this problem and reduce consumption of junk food, in order to prevent obesity in students and improve their health and quality of life. In this way, the aim of the present study was to analyze the relationship between the consumption of junk food and the physical complex in university undergraduates of three degrees of health.

Methods

Design of Study between the

characteristics of anthropomorphic analysis and the consumption of junk food in university undergraduates. Before taking the surveys, the objectives of the research were presented. Each questionnaire was accompanied by informed consent. The participants read and signed the informed consent where they expressed their acceptance to participate in the study.

Study sample

The present research was a descriptive and observational study that allowed us to define the relationships

The study included a total of 135 volunteers university undergraduates, aged 19-22 years. They were 79 undergraduates in bachelors of Physiotherapy (BPh), 34 in Nursing (BNu) and 48 in Psychology (BPs) of Universidad Vizcaya de las Am?ricas, campus Tepic Nayarit Mexico. The students who participated were enrolled in the four-month period 2018-II and showed their written consent to participate in the research. The project used a survey of frequency of consumption of junk food during school hours. Subsequently, an anthropomorphic analysis of the participants was carried out.

Anthropometric assessment

The anthropomorphic assessment (height, weight, BMI, Waist circumference, hip circumference, and waist-hip ratio) was measured using standard methods. Students were wearing light indoor clothing. Height (m) was measured using a height meter (Seca, model 786, Germany) and body weight (Kg) was measured to the nearest 0.1 kg using a digital scale (Omron HBF-514C, USA) with a capacity of 150 Kg. The body mass index (BMI) was determined their respective heights and weights using the

relation: weight / height (Kg/m²). From these BMI values, normal weight, overweight, and kind of obesity were determined using the World Health Organization (WHO)⁷. For the determination of waist circumference (WC), students were placed in a standing position with the abdomen and arms relaxed alongside the body, and a flexible measuring tape (1 mm accuracy) was held horizontally at the midpoint between the bottom edge of the last rib and the iliac crest, and it was classified as normal or elevated according to procedures recommended by the WHO (7-8). Hip circumference (HC) was measured at the maximum point below the waist, without compressing the skin. Waist-hip ratio (WHR) was calculated by dividing the waist measurement by the hip measurement.

Statistical analysis

The data obtained was presented using tables and bar charts, frequency proportion. Chi-square was used to analyse the difference in these categorical variables: junk food intake, BMI, WC, and WHR of students. Junk food and anthropometrics between students undergraduate was analyzed by Pearson Correlation Coefficient. The Statistica version 10 software package was used for statistical analysis.

Results

Junk food intake

A total of 161 volunteers university undergraduates participated in a survey on the consumption of junk food. Students from BNU and BPs were always consuming the most junk food with 68.6% and 67.3%, respectively (Figure 1). However, BPh students consume them frequently (30.5%) and sometimes (33.7%). In contrast, few students of BPh.

BNU, PDs rarely or never (4.6%, 5.1%, 1.5%, respectively) consume this kind of food. In such a way, junk food is generally consumed inside of the University and in the street food stall that are around the university (Figure 2).

Table 1 shows the consumption of the kind of junk food that students consume during school hours. Cookies and pizza are the foods most consumed by BPh students with 87.05% and 86.71%, respectively, followed by chips (66.97%), tacos (64.58%) and bubble gum (61.08%). BNU students tend to consume chips (82.40%), bubble gum (74.05%), pizza (60.14%) and hamburgers (52.35%). Hamburgers, tacos, cookies, and pizza are the junk foods frequently consumed by BPs students, at 79.46%, 67.50%, 62.32% and 61.25%, respectively.

Table 2 shows that soft drinks have a higher percentage of consumption by students of the three bachelor's degrees, followed by processed juices for BPh (49.32%) and BPs (53.04%) and milkshakes for BNU (61.62%).

Anthropometric assessment

The anthropometric measurements of the university undergraduates were analyzed, showing that 92.42% of the BPh students have an average weight of 73.01Kg, whereas the BMI, WC and WhR were similar in the three degrees (Table 3) with >25 Kg/m², >80 cm, >95 cm, respectively. Thus, 73.53% of BNU students presented normo-weight, however, in BPh and BPs presented overweight with 64.55% and 75.00%, respectively. Therefore, a Pearson correlation was analyzed to see if there was a relationship between junk food consumption and anthropometric measurements (Table 5). This table shows that there is a correlation between junk

food with weight, BMI, WC and WhR in all bachelors.

Discussion

This study explored the interrelationships among junk food and anthropomorphic indices among undergraduate students of the Universidad Vizcaya de las Americas in Nayarit Mexico. This investigation describe the impact of the consumption of junk food in-take inside an university institution. Most studies report the impact of junk food consumption on children's eating habits as they consume it in schools (elementary school, middle school, and high school) or in by the little shops (tienditas as it calls in Mexico) around them^{6,9-10}. In this study it was observed that students can easily acquire this type of food within the installation of their university, which reflects an alarming reality compared to other studies, mainly in schools where these types of products are supplied, indirectly forcing a greater consumption of them, causing the development of diseases derived from weight gain (hypertension, type 2 diabetes mellitus, dyslipidemia, obesity)¹¹⁻¹³. In addition, some studies have reported a positive correlation between consumption of junk food and weight gain in people, as shown in the present study (Table 5)¹⁴⁻¹⁶. When comparing junk food intake in this study with other research, the results revealed that the average junk food intake of university students was three times that of Bangladesh and Nepal, similar to the United States, and twice as many Latin American countries^{15,16-18}. In this sense, the ingredients that make up junk food consumed during school hours are high in calories (>1200KJ), carbohydrates (>65 g/100g), and lipids (>20 g/100g)¹⁹⁻²¹. In addition, increasing sedentary lifestyle,

the economic status, nutritional culture of students and parents, or combination of these factors also play a decisive role in the consumption of this type of food, and it can bring health problems^{4,6,9}. Greenwood and Sanford²² observed that eating habits interfere with weight gain for college students because of easy access to fast food and the cafeteria that prepares high-calorie foods²³. Hellmich²⁴ reported that college men had a higher percentage of weight gain from freshman to senior year than college women. Importantly, the (morning, afternoon) shift of school hours impacts students' dietary choices and the environment in which they find themselves²⁵.

On the other hand, from the point of view of Mexican politics, there are government programs (School Breakfast Program, Food Support Program, Liconsa Program, others) that have been proposed to help reduce bad food environments and combat obesity²⁶. However, these programs have only focused on children and young people, and university communities have been disadvantaged, which could focus on actions that enhance the consumption of nutritious and healthy foods. Therefore, it is important to emphasize that the health of university undergraduate is also important to take care to prevent metabolic syndrome diseases such as obesity, cardiovascular disease and diabetes mellitus²⁷⁻²⁸.

Conclusion

The results showed a high frequency of consumption of junk food inside the University of Vizcaya de las Americas. More than half of the university students who consume junk food were overweight. There was a relationship between the intake of junk food and the BMI of the

students. Therefore, recommendations for future research include a longitudinal study that examines the variation in consumption of these foods from entry to completion of their studies to better understand how college life can influence eating habits that led to weight gain.

Acknowledgements

The authors thank the students of the Universidad Vizcaya de las Américas campus Tepic for participating in the evaluation. We would also like to thank the coordinators of the Bachelor's degrees of the same University for facilitating the space to carry out the surveys. Likewise, the authors thank the coordinator of the nutrition bachelor, MNC, Hugo David Rodriguez Jimenez, for the authorization of the Nutrition Laboratory space. Finally, we thank the XXIII Verano de

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Ethical Standards

This study used retrospective survey data and did not include any animal or human experiments.

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Tables

Table 1: Frequency distribution of junk food consumption by students undergraduate during school hours.

Junk Food	BPh	BNu		BPs
		Consumption (%)		
Tacos	64.58 ^a	46.03 ^b		67.50 ^a
Hamburgers	58.42 ^b	52.35 ^b		79.46 ^a
Patties	16.82 ^a	15.87 ^a		19.25 ^a
Hotdogs	27.05 ^a	27.20 ^a		26.79 ^a
Pizza	86.71 ^a	60.14 ^b		61.25 ^b
Treats	28.08 ^a	30.15 ^a		18.75 ^b
Fried foods	57.39 ^a	40.15 ^b		50.00 ^a
Pan	42.77 ^a	21.56 ^b		42.14 ^a
Doughnuts	17.46 ^a	16.91 ^a		17.86 ^a
Hot cakes	25.00 ^b	27.94 ^b		33.21 ^a
Cookies	87.05 ^a	46.03 ^c		62.32 ^b
Pastries	23.28 ^a	28.67 ^a		18.75 ^a
Ice cream	36.80 ^a	39.42 ^a		24.06 ^b
Chips	66.97 ^b	82.40 ^a		54.56 ^c
Bubble gum	61.08 ^b	74.05 ^a		59.37 ^c

BPh: Bachelor of Physiotherapy; BNu: bachelor of Nursing; BPs: Bachelor of Psychology. Uppercase letters indicate significant difference between bachelor.

Table 2: Frequency distribution of beverage consumption by university undergraduates during school hours.

Junk food	BPh	BNu		BPs
		Consumption (%)		
Soft drinks	66.03 ^b	81.91 ^a		60.89 ^b
Energized drinks	36.37 ^b	37.94 ^b		44.82 ^a
Processed juice	49.32 ^a	50.74 ^a		53.04 ^a
Natural juice	26.89 ^a	21.47 ^a		18.74 ^a
Coffee	21.92 ^b	25.00 ^b		30.36 ^a
Beer	22.60 ^a	21.32 ^a		20.54 ^a
Milkshakes	21.92 ^b	61.62 ^a		19.64 ^b

BPh: Bachelor of Physiotherapy; BNu: bachelor of Nursing; BPs: Bachelor of Psychology. Uppercase letters indicate significant difference between bachelor.

Table 3: Distribution of anthropometric assessment by university undergraduates.

Anthropometric assessment	Bachelor					
	BPh		BNu		BPs	
	Average	Frequency proportion (%)	Average	Frequency proportion (%)	Average	Frequency proportion (%)
Height (m)	1.66	97.71 ^a	1.65	96.82 ^a	1.60	94.28 ^a
Weight (Kg)	73.01	92.42 ^a	68.51	91.52 ^a	63.93	82.33 ^b
BMI (Kg/m ²)	26.19	66.84 ^b	25.11	51.73 ^c	24.86	88.78 ^a
WC (cm)	88.45	77.16 ^a	83.87	76.68 ^a	77.94	78.35 ^a
WHR	98.13	78.42 ^a	97.64	77.17 ^a	98.53	79.05 ^a

BPh: Bachelor of Physiotherapy; BNu: bachelor of Nursing; BPs: Bachelor of Psychology; BMI: body mass index; WC: Waist circumference; WHR: waist-hip ratio. Uppercase letters indicate significant difference between bachelor.

Table 4: Prevalence of obesity as per body mass index (BMI), weight circumference (WC), and weight-hip ratio (WHR) of university undergraduates.

	BPh		BNu		BPs	
	n	%	n	%	n	%
UW	nd	0	nd	0	nd	0
NW	28	35.44 ^b	25	73.53 ^a	11	25.00 ^b
OW	51	64.55 ^b	9	26.47 ^c	37	75.00 ^a
Ob	nd	0	nd	0	nd	0

BPh: Bachelor of Physiotherapy; BNu: bachelor of Nursing; BPs: Bachelor of Psychology; BMI: Body mass index; UW: underweight; NW: normal weight; OW: overweight; Ob: obesity. nd: non-detectable. Uppercase letters indicate significant difference between bachelor.

Table 5: Correlation of junk food intake with anthropometric assessment variables using Spearman’s rank order and Pearson correlation.

		Bachelor					
		BPh		BNu		BPs	
		r ²	p	r ²	p	r ²	p
Junk food	Height	0.0026	0.2512	0.0214	0.1862	0.0021	0.248
	Weight	0.9045	0.036	0.7645	0.044	0.9325	0.022
	BMI	0.8914	0.026	0.8473	0.047	0.9614	0.013
	WC	0.8862	0.047	0.9275	0.019	0.9589	0.04
	WHR	0.7690	0.052	0.7985	0.029	0.7935	0.05

BPh: Bachelor of Physiotherapy; BNu: bachelor of Nursing; BPs: Bachelor of Psychology; BMI: body mass index; WC: Waist circumference; WHR: waist-hip ratio.

Figures

Figure 1: Percentage distribution of consumption of junk food.

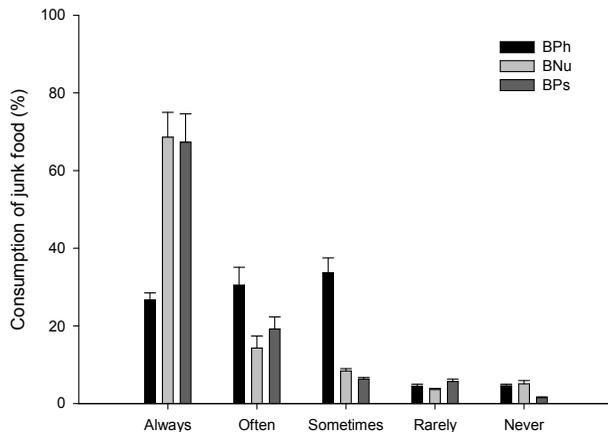
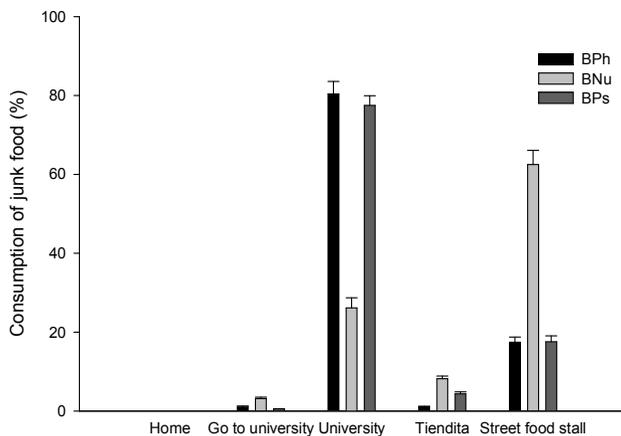


Figure 2: Places of frequency of consumption of junk food.



Sensitization Of Women Suffering From Infertility To Natural Allergens

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Abstract: Now, in connection with deterioration of ecological conditions, development of the chemical industry and wide use of various products causing allergy, in agriculture, food and chemical industry, sharp increase of sensitization of an organism of people influencing a condition of their health is established. Thus, the frequency of allergic dermatitis, allergic asthma, allergic bronchitis, rhinitis, vasculitis has increased dramatically.

Keywords: Keywords: infertility, antibodies, sensitization.

Relevance. Now, in connection with deterioration of ecological conditions, development of the chemical industry and wide use of various products causing allergy, in agriculture, food and chemical industry, sharp increase of sensitization of an organism of people influencing a condition of their health is established. Thus, the frequency of allergic dermatitis, allergic asthma, allergic bronchitis, rhinitis, vasculitis has increased dramatically. At present there are a huge

number of people with hypersensitivity to foodstuffs, household chemicals, antibiotics, various plants, etc. From these points of view, it becomes clear that hypersensitivity to various allergens, everywhere surrounding each person, cannot but affect the overall health and reproductive function of the person. [1, c.1]. At present, there is evidence of infertility development in the literature in connection with the emergence of a woman's tolerance to her husband's

sperm, associated with sperm agglutination and reduced mobility through cervical mucus, capitation [1, p.5-6; 2, p.87-88; 3, p.814], which is characteristic of the development of specific IgG4 together with IgG1 [1, p.3; 4, p.20-21]. Also, activation of the components of the seed liquid with the appearance of antisperm antibodies [5, p. 351-352] has been established.

The purpose of our study was to assess the sensitization profile of women of fertile age suffering from infertility to the spectrum of allergens of animal and plant origin.

Materials and methods. The work was carried out in the International Center of Molecular Allergology on the basis of the Center of Advanced Technologies (Tashkent, Uzbekistan).

Forty women (the main group) aged 24 to 40 years (average age 29.5±2.4 years) living in Bukhara (Uzbekistan) took part in the study with a diagnosis of infertility. The control group consisted of 20 healthy

women of the same age residing in the same region. Written informed consent was obtained from all the patients for the study.

The criteria for inclusion in the study were patients with infertility (primary and secondary) of infectious or mixed genesis. The exclusion criteria were patients with infertility of hormonal genesis, severe somatic pathology and allergic diseases.

The serum was tested with the ALEX allergotest (MADx, Austria) according to the manufacturer's instructions. Patients with IgE-specific levels of at least 0.1 kU/L were considered positive. Analysis of IgE-sensitization profiles to allergenic molecules was performed using IBM SPSS 20 and Microsoft Excel.

Results of the study and discussion. A comparative analysis was carried out for 20 allergenic molecules and animal epidermis extracts: cats, dogs, rats, mice, cows, goats, sheep, horses, pigs, rabbits, guinea pigs and hamsters (Table 1).

Table 1

List of allergenic molecules and animal extracts for testing women suffering from infertility

Animalspecies	Scientifictitle	Molecule
Cat	Felisdomesticus	
Cat	Felisdomesticus	rFel d 1
Cat	Felisdomesticus	rFel d 2
Cat	Felisdomesticus	rFel d 4
Cattle	Bosdomesticus	
Cattle	Bosdomesticus	rBos d 2
Dog	Canis familiars	
Dog	Canis familiars	rCan f 1
Dog	Canis familiars	rCan f 2

Dog	Canis familiars	rCan f 3
Goat	Capra hircus	
Guineapig	Caviaporcellus	
Hamster	Cricetuscricetus	
Horse	Equuscaballus	
Horse	Equuscaballus	rEqu c 1
Mouse	Mus musculus	nMus m 1
Pig	Susdomesticus	
Rabbit	Oryctolagus spp.	
Rat	Rattusnorvegicus	
Sheep	Ovisaries	

Sensitization to 16 allergic molecules and food extracts of animal origin, in particular, molecules of chicken protein and egg yolk, cow's milk of camels, goats, horses and sheep, as well as allergens of chicken, turkey, beef, lamb, horsemeat were also assessed (Table 2).

Table 2

List of allergenic molecules and food extracts of animal origin for testing women suffering from infertility

Product	Scientific name	Molecula
Camelmilk	Camelusdromedarius	
Cow'smilk	Bosdromedarius	
Cow'smilk	Bosdromedarius	nBos d 4
Cow'smilk	Bosdromedarius	nBos d 5
Cow'smilk	Bosdromedarius	nBos d 8
Goat's milk	Capra hircus	
Horse's milk	EquusCaballus	
Sheep's milk	Ovisaries	
Cow'smilk	Bosdomesticus	
Cow'smilk	Bosdomesticus	nBos d 6
Chicken meat	Gallus domesticus	
Horse meat	Equuscaballus	
Sheep meat	Ovisaries	
Pig meat	Susdomesticus	
Rabbit meat	Oryctolagus spp.	
Turkey meat	Meleagrisgallopavo	

Among the examined patients, 28 (70%) suffered from primary infertility and 12 (30%) from secondary infertility. The duration of infertility was from 3 to 10 years. In Vitro Fertilization was applied in 7 (17, 5%) patients. Allergic anamnesis was observed in 22 (55.0%) patients from the main group and 3 (15.0%) women from the control group. In the main group of women there were 9 (22,5%) patients with antibiotic allergies.

As a result of the conducted studies it was established that in the main group (Table. 1-A) 8 (20%) women with infertility demonstrated sensitization to the allergenic molecule Fel d 2, which is a cat's albumin, 7 (17.5%) women had IgE to the cow's epidermis (Bos d epithelia). One woman reacted to the goat's epidermis, guinea pigs and hamster to each allergen 3 (7.5%).

No IgE sensitization and clinically significant reaction to the respiratory allergens of the animal epidermis was detected in the control group women. The exception was cat molecules Fel d 1 and Fel d 2, to which IgE was detected in one woman of this group (5.0%). The average IgE level to Fel d1 and Fel d2 in the group was 0.3 and 0.02 kU/L, respectively. The median was zero. Patients of the control group were also immunologically tolerant to all studied molecules and food extracts of animal origin (Fig. 1-B).

Sensitization to food allergens of animal origin in women of the main group was expressed in the presence of

specific IgE to beef 9 (22.5%), to horsemeat - 8 (20.0%), to rabbit - 4 (10.0%). In addition, 2 (5.0%) women were sensitized to the ovomucoid of the chicken protein Gal d 1 to the ovotransferrin Gal d 3.

Thus, a group of women with infertility (the main group) demonstrated a profile of sensitization to allergens of animal origin, which differs significantly from the profile of women in the control group. It was found out that 8 (20,0%) patients with infertility were characterized by sensitization to cat's albumin, to cow's meat and epidermis.

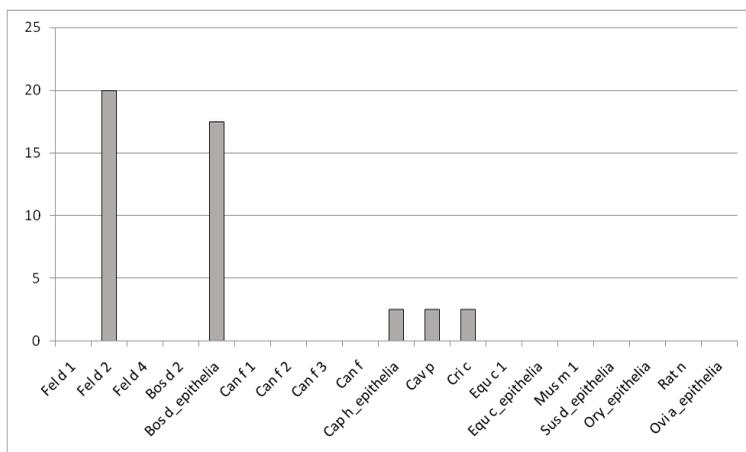
On the basis of the obtained results it is possible to propose a hypothesis that for a part of women with infertility allergic reactions to animal allergens are characteristic. The presence of homologous epitopes of allergens with human antigens may cause cross-reactions, support allergic inflammation, and probably lead to reproductive dysfunction in women.

In turn, the use of molecular allergology methods in the comprehensive examination of patients with infertility can be an additional method for the diagnosis of allergic sensitization of women. All this gives an opportunity to look at the pathogenesis of infertility in a different way and, of course, to reconsider the approaches to the diagnosis and treatment of infertility. Also, allergic sensitization to animal protein should be considered when carrying out artificial insemination, taking into account the use of bovine albumin in this procedure.

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Table 1-A
General profile of sensitization of patients with infertility to animal allergens (n=40)



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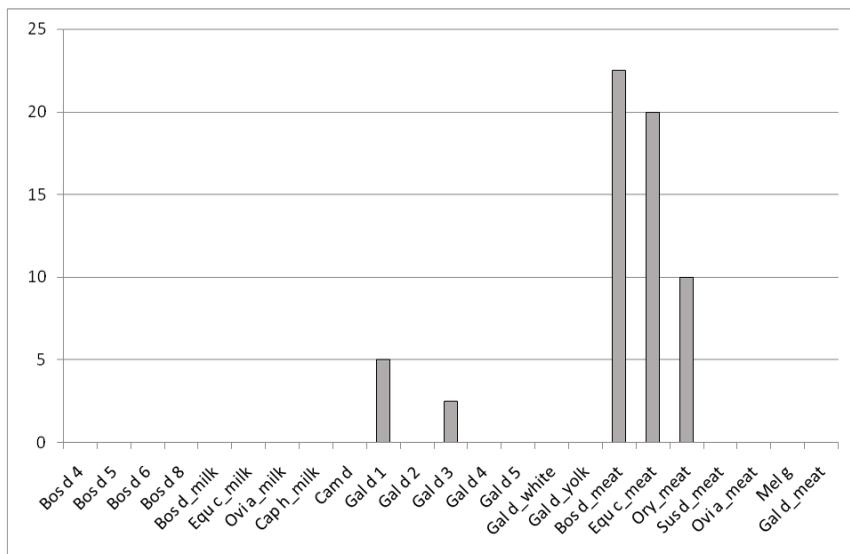
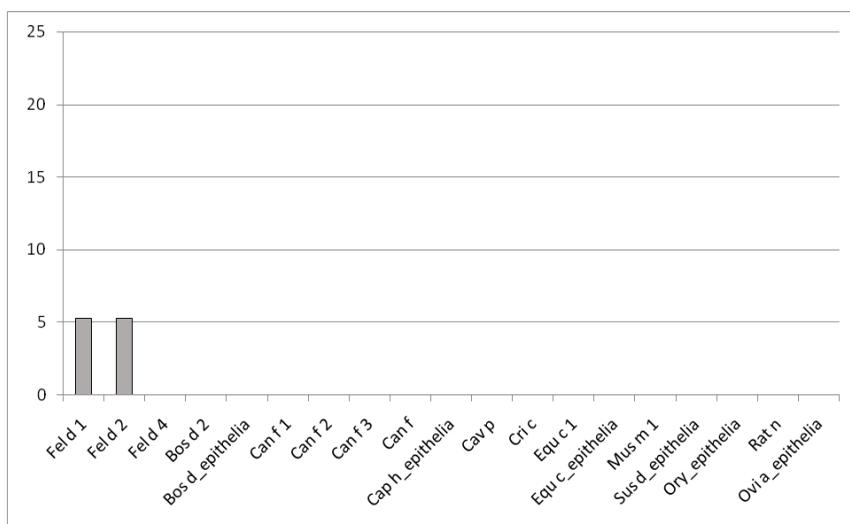
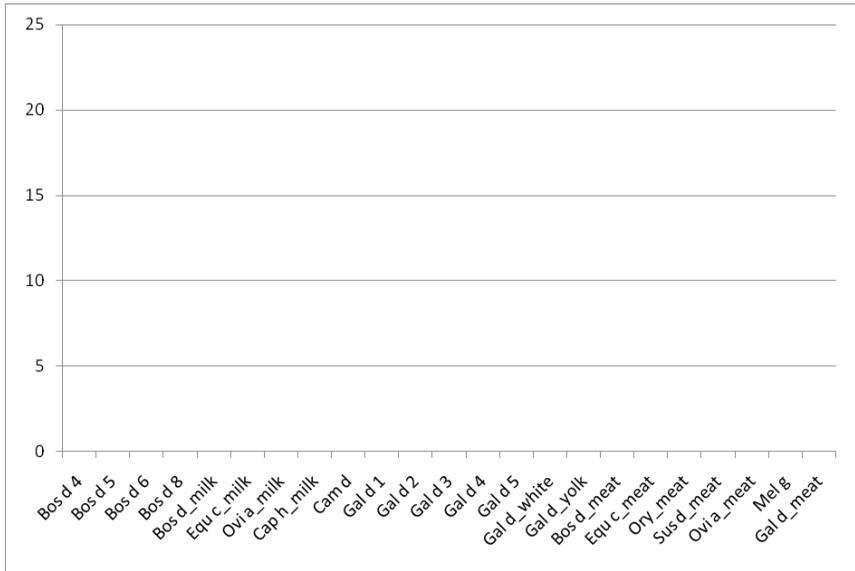


Figure 1-B
General profile of sensitization of control group patients to animal allergens (n=20)





Novel strain of Hepatitis C Virus genotype 1b in an HumanImmunodeficiency Virus (HIV) infected patient in BeninCity, Nigeria

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Bankole Henty Oladeinde, Ifeoma Mercy Ekejindu, Richard Omoregie, Ikpomwonosa Odia, Obiora .D. Aguh. Novel strain of Hepatitis C Virus genotype 1b in an HumanImmunodeficiency Virus (HIV) infected patient in BeninCity, Nigeria. *Journal of research in health science*. Volume 3 issue. 5-6, 2019, pp. 38-46



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Background: HCV disease severity and treatment outcome are affected by circulating genotype. Genotypic prevalence of HCV among HIV infected patients in Nigeria is unknown. Against this background this study aimed at determining the genotypic prevalence of HCV among HIV infected patients in Nigeria

Study design: This was a cross sectional study.

Methods: Sera from 564 HIV infected and 250 non-HIV patients were screened for antibodies to HCV using immuno-chromatographic test kits, followed by detection of HCV ribonucleic acid (HCV-RNA) and sequencing of resulting amplicons using standard molecular techniques.

Results: HIV was not significantly associated with HCV sero-positivity ($P = 0.682$). Only 1 (16.6%) of all six HIV infected patients with anti-HCV had detectable HCV-RNA in serum, and the isolate was identified as HCV genotype 1b, which did not cluster around other HCV genotype 1b isolates of Nigerian origin.

Conclusions: This study reports a novel strain of HCV genotype 1b in Nigeria

Key words: Hepatitis C Virus genotypes, HIV infected patients, Nigeria

INTRODUCTION

The human immunodeficiency virus (HIV) infection is associated with increased mortality and morbidity worldwide, with prevalence rates that vary from region to region. It is a global health challenge with attendant medical, economic and social implications. [1] Globally, Sub-Saharan Africa has the highest burden of HIV infection accounting for about two-thirds of all people living with HIV in the world. [1] HIV is endemic in Nigeria, as reports indicate that only two countries namely South Africa and India have more people living with HIV than Nigeria in the world. [2]

All over the world, Hepatitis C virus (HCV) infection is a major public health problem. HCV is the major etiological agent of chronic hepatitis worldwide. [3] Up until 2014, only six HCV genotypes designated 1 - 6 were identified. [4]. However a new genotype designated HCV genotype 7 was recently identified in Central Africa [5]. HCV infection is reported to be common among HIV infected patients due to similar route of transmission shared by both viruses. [6] Reports show that about 20% of HIV negative patients infected with HCV naturally clear HCV from their system. [7] Clearance of HCV occurs in only about 5% of HIV positive patients. [7] making them present with high risk of developing HCV liver related diseases than HCV mono-infected patients.

The standard treatment for HCV is pegylated interferon alfa (PegIFN) plus ribavirin. [8] Recently, however, new directly acting antiviral drugs which results in a higher sustained virological response rate have been used in treatment of HCV infected patients. [9] Treatment outcomes

of HCV infected patients are known to be affected by specific HCV genotypes. [10] HCV genotypes 1 and 4 are generally reported to be more resistant to treatment with pegylated interferon alfa plus ribavirin than HCV genotype 2 and 3. [11] Also the severity of HCV related liver diseases has been shown to be associated with specific HCV genotypes, [12] with HCV genotype 1 incriminated in more severe form of liver diseases than the rest. [13]

Although free HIV tests and management services are provided in many hospitals in Nigeria, routine screening for HCV infection is not done, neither is specific HCV treatment offered to patients. [14] This is likely to result in missed diagnosis of HCV infection which over time could progress to other serious medical complications including death of patients. No data presently exist on the genotypic and subtype prevalence of HCV among HIV infected patients in Nigeria. Qualitative detection of HCV-RNA is used for confirmation of HCV infection. [15] This is not done in most clinical settings in Nigeria, as diagnosis often relies on detection of antibodies to HCV in sera. Against this background, this study aimed at determining the HCV genotypic and subtype prevalence among HIV infected patients in Benin City, Nigeria.

METHODS

Study Area

This study was carried out in the University of Benin Teaching Hospital, which is a public tertiary health institution with referral status located in the South-South geographical region of Nigeria.

Study population

Two sets of subjects (comprising of 564

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HIV infected and 250 non-HIV infected patients) were recruited using a random sampling technique from the University of Benin Teaching Hospital for this study. Of the 564 HIV infected patients enlisted in this study, 133 were highly active antiretroviral therapy (HAART)-naïve while the remaining were HAART-exposed patients. Informed consent was obtained from all subjects prior to specimen collection. Consent was obtained from parents or guardians of minors. A questionnaire was used to obtain relevant information from study participants. Approval for study was gotten from the Ethics and Research Committee of the University of Benin Teaching Hospital, Benin City. Protocol number: ADM/E 22/A/VOL. VII/1014.

Specimen collection and processing

Five milliliters of blood was collected from all participants and dispensed into plain containers. All subjects were screened for the presence of antibodies to HCV using an immunochromatographic kit - Clinotech Anti-HCV (Clinotech Diagnostics, Richmond, Canada) following the manufacturer's instruction. Two milliliters of all HCV seropositive sera was placed into cryovials and stored at - 80 °C for further molecular studies.

Detection of HCV-RNA

HCV-RNA was extracted from 140 µl of patients sample with the use of Zymo ZR Viral DNA/RNA kit. The RNA was eluted in 50 µl DNase/RNase free water and subsequently used for genome amplification of the 5' untranslated region (UTR) region of HCV by Reverse transcription polymerase chain reaction (RT-PCR) using OneStep RT-PCR kit (New England Bio Labs). One Step RT-PCR kit components were thawed and

mixed by inverting several times. The reaction mixture contained 12.5 µl of One Taq one-step reaction mix (2x), 1 µl of One Taq one-step enzyme mix, 1 µl of forward primer 5' CTGTGAGGAACTACTGTCTT-3', 1 µl of reverse primer 5' ATACTCGAG GTGCACGGTCTACGAGACCT-3', 2.5 µl of RNA extract and 7 µl of nuclease free water to give a final volume of 25 µl. Amplification was initiated with the Eppendorf Thermocycler. The cycling conditions for the RT-PCR were as follows: an initial cycle at 50°C for 30 min and 95°C for 15 min; followed by 45 cycles at 95°C for 30 s, 50°C for 30 s and 72°C for 1 min; and a final extension at 72°C for 10 min. The amplified products were visualized after electrophoresis on an ethidium bromide stained 1.5% agarose gel. Sequencing was done at Inqaba Biotec West Africa, South Africa (a commercial biotech company) Using ABI 350XL sequencer. True HCV infection in this study was defined as the presence of HCV-RNA in patients' sera. [15]

Characterization of HCV isolate

Sequence output of ABI 3500XL analyser (chromatogram) was opened to reveal nucleotide sequences using the software FinchTV available at <http://www.geospiza.com/ftvdlinfo.html>. The identity of aligned HCV sequence was confirmed using the BASIC LOCAL ALIGNMENT SEARCH TOOL (BLAST) available at the National Center for Biotechnology information (NCBI). Confirmed HCV isolate was compared with known genotypes (1-6) in GenBank database and HCV subtyping was performed using the Oxford

HCV automated subtyping tool version (2.0). Phylogenetic trees created by the neighbour-joining method of this study isolate and 44 HCV isolates from different countries were done as previously described. [16,17]

Data Analysis

Analysis of data was carried as appropriate using the statistical software INSTANT® (Graphpad Software Inc., La Jolla, CA, USA). P < 0.05 was considered significant.

RESULTS

The sero-prevalence of HCV in this study was 0.9%. HIV status was not significantly associated with HCV sero-positivity (OR=2.677, 95%CI=0.321, 22.368; p=0.682) (Table 1). Of the 6 HIV/

HCV sero-positive patients found in this study, only one HAART-naïve patient had detectable HCV-RNA (Table 2). Generally, HAART naïve HIV infected patients had a 9 times insignificantly higher risk (HAART naïve vs. HAART exposed: 50.0% vs. 0.0%; OR = 9.000, 95% CI = 0.2233, 362.81. P = 0.333) of acquiring true HCV infection than their HAART exposed counterparts. True HCV infection was found in only one HAART naïve HIV infected male patient (Table 2).

Molecular characterization of HCV isolate showed that it was HCV genotype 1b. Phylogenetic analysis revealed that study strain did not cluster around any previous HCV genotype 1b of Nigerian origin, but was found to be a close relative of one with an Indian descent (Figures 2 and 3).

Table 1: Sero-prevalence of HCV infections among study population

Characteristics	N	No. HCV Sero positive (%)	OR	95% CI	P value
HIV status					
HIV Positive	564	6(1.1)	2.677	0.321, 22.368	0.682
HIV Negative	250	1 (0.4)			
	814	7 (0.9)			

N- number of patients examined, HCV - hepatitis c virus, OR- odd ratio, CI- confidence interval

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Table 2: Prevalence of true HCV infection among study population

Characteristics	N	No. HCV-RNA Pos (%)	OR	95% CI	P value
HBV Sero-positive					
HIV Positive	6	1(16.7)	0.818	0.0207, 32.295	1.000
HIV Negative	1	0 (0.0)			
HAART status					
HAART Naïve	2	1 (50.0)	9.000	0.2233, 362.81	0.333
HAART Exposed	4	0 (0.0)			
Gender					
Male	1	1 (100.0)	33.000	0.440, 2478.2	0.1667
Female	5	0 (0.0)			

N- number of patients examined, HCV-RNA - hepatitis c virus ribonucleic acid, OR- odd ratio, CI-confidence interval

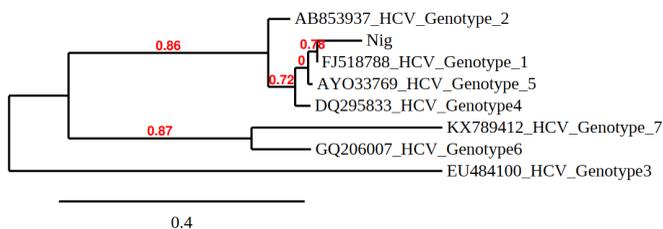


Figure 2: Genotypic characterization of Hepatitis C virus isolate from study

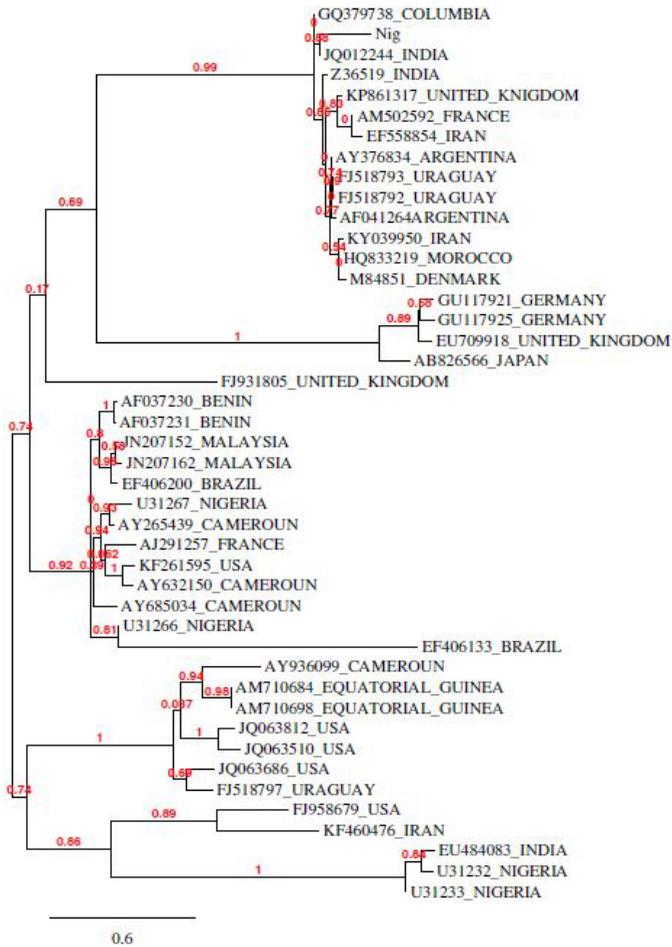


Figure 3: Phylogenetic analysis of study HCV isolate and HCV/1b isolates retrieved from Genbank

DISCUSSION

HCV disease severity is reported to be affected by circulating genotypes and subtype. [10] There is a dearth of knowledge on the prevalence of HCV genotypes among Nigerian patients. Indeed, no data presently exist on the genotypic prevalence of HCV among HIV infected patients in Nigeria. Against this background this study was conducted.

Irrespective of HIV status, an overall HCV sero-prevalence of 0.9% was observed in this study. HIV infected patients were found to have a HCV sero-prevalence of 1/1% which is lower than values reported in some studies, [18, 19], but higher than another reported elsewhere. [14]. The sero-prevalence of HCV is known to differ from place to place even within the same country. [20] This may explain the finding in this study.

HIV non-infected patients had a HCV sero-prevalence of 0.4%, a value lower than 4.4% reported in a previous Nigerian study among a similar population. [21] In this study, HIV positive patients were observed to have a 2.6 times greater risk of being HCV sero-positive than their HIV negative counterparts. A similar finding has been reported in two other African studies. [22, 23] Molecular analysis of all seven subjects with antibodies to HCV, showed that only 1 (16.7%) HIV infected patient had detectable HCV-RNA. Much higher values have been reported in other studies. [24, 25] The observed variation may be due to differences in location, molecular diagnostic technique used, host genetic factors and target genes assayed for in these studies.

HAART na?ve HIV/HCV sero-positive patients were found to have about 9 times higher risk of having a true HCV infection

than HAART exposed patients. It is generally acknowledged that a healthy CD4+ cell response is central to the control of HCV infection. It is possible that the use of HAART among HIV/HCV sero-positive patients may have resulted in a significant reduction in HIV viremia and increase in CD4+ count, factors that are associated with reduction in HCV-RNA levels in a previous study. [26] The gender-wise prevalence of true HCV infection showed that males had about 33 times higher risk (OR= 33.00) of acquiring true HCV infection than females. HCV clearance among women is reported to be associated with high level of estrogen. [27] This may account for the pattern of result observed among females in this study.

Genotypic characterization of HCV isolate in this study revealed that it was genotype 1. Other studies have reported HCV genotype 1 as the predominant genotype in Nigeria. [28-29] With respect to subtype identity, the HCV genotype 1 isolate was found to belong to subtype class b. It is important to note that past studies have reported HCV genotype 1b among Nigerian populations. [28-29] One French study has reported an association between HCV genotype 1b and transfusion of blood and blood products. [30] Indeed, the patient with HCV genotype 1b in this study claimed to have been transfused with blood in the past.

Phylogenetic analysis of HCV isolate obtained in this study with 44 other HCV genotype 1b reference strains showed that the HCV isolate from this study did not cluster around HCV genotype 1b isolate of Nigerian origin, indicating that it is a new strain of HCV genotype 1b circulating in Nigeria. Study HCV isolate was found to be a close relative of an Indian strain

with Genbank accession number JQ012244, suggesting that it may have been imported into the country. To our knowledge this is the first study in Nigeria to report HCV genotype and subtype among HIV infected patients. The Nigerian studies highlighted above were done among populations with unknown HIV status. The sequence of HCV isolate from this study has been deposited in Genbank database with the accession number KY852360.

CONCLUSIONS

The sero and true prevalence of HCV infection was higher among HIV infected

subjects than their uninfected counterparts. One HIV infected patient was found to harbor a strain of HCV genotype 1b, which did not cluster among other HCV genotype 1b isolates of Nigerian descent. This study underscores the presence of a new variant of HCV genotype 1b in Nigeria.

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Hypothesis For Pathogenesis: Connection Between Immune, Nervous And Endocrine System

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Abstract: This hypothesis suggests that disturbance of the balance between the three systems (immune system, endocrine system and nervous system) may cause physiological diseases. Nervous system, endocrine system & immune system are extensively interconnected and influence each other. So strong is their influence that any disturbance in the balance between these three systems may cause physiological diseases. In other ways, monitoring these systems can help us discover the pathogenesis of several diseases.

Keywords: Immune system, Nervous system, Endocrine system.

INTRODUCTION

Recent advances in medical science show link between immune system, endocrine system and nervous system. This hypothesis suggests that disturbance of the balance between the three systems (immune system, endocrine system and nervous system) may cause physiological diseases. If there is an immune disorder, we need to monitor endocrine and nervous system as well to discover the pathogenesis of the disease. Similarly, in endocrine or nervous physiological diseases, we have to monitor the

respective other systems, then we can find the proper cause of that disease. By studying recent research papers, we found extensive correlation between the three systems of our body; they are nervous system, endocrine system and immune system.

CONNECTION BETWEEN IMMUNE & NERVOUS SYSTEM:

There is elaborate interactions between immune and nervous systems. [1] Sympathetic and parasympathetic nervous systems are well connected to lymphoid organs and

influence them. Also, neurotransmitters such as acetylcholine, norepinephrine, nasoactive intestinal peptide, substance P & histamine modulate immune activity.

On the other hand, immune system modulates brain activity, including body temperature, sleep & feeding behaviour.

CONNECTION BETWEEN ENDOCRINE & IMMUNE SYSTEM:

Recent advances suggest that immune system does not function in isolation but is influenced by other physiological systems such as endocrine and neuro-endocrine system. [2]Immune function is altered by neuroendocrine peptide, sex

hormone and Vitamin D metabolites. (Vitamin D is actually a hormone than a vitamin. Body makes most Vitamin D it needs, only 10% comes from food).

CONNECTION BETWEEN ENDOCRINE & NERVOUS SYSTEM:

Similarly, there is link between endocrine and nervous system.[3]Human behaviour influences neural inputs in hypothalamus. Hypthalamus send signals to pituitary to regulate endocrine glands. Hormonal feedback from these glands regulates behaviour and mood. Thus endocrine and nervous system influence each other.

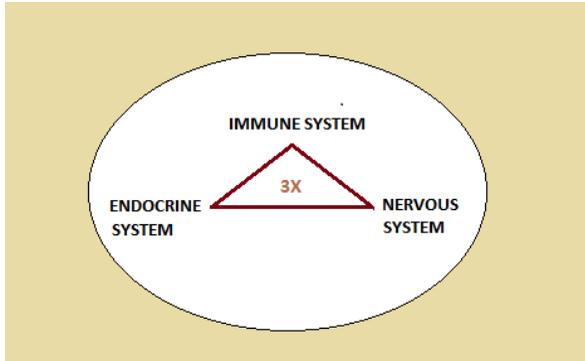


Figure 1. Connection between the systems

HYPOTHESIS

Nervous system, endocrine system & immune system are extensively interconnected and influence each other. So strong is their influence that any disturbance in the balance between these three systems may cause physiological diseases (not caused by microorganisms or cancer). Cause of several physiological diseases like asthma, Parkinson's disease, etc. has not yet been discovered. If there is an immune disorder physiological

disease, we have to monitor endocrine and nervous system as well. Then we can find the proper cause of that disease. Similarly, in endocrine or nervous physiological diseases, we have to monitor the respective other systems.

MEDICAL IMPLICATIONS

Parkinson's Disease

- Estrogen deprivation leads to the death of dopamine cells in the brain. The majority of clinical reports support an

antidopaminergic effect of estrogens on Parkinsonian symptoms.[4]

- When nitric oxide is produced within the brain in excess by a protein called inducible nitric oxide synthase (iNOS), neurons start dying.

After castration, levels of iNOS and nitric oxide increase in the brain. Interestingly, castration does not cause Parkinson's-like symptoms in male mice deficient in iNOS gene, which indicates that loss of testosterone causes symptoms via increased nitric oxide production.[5]

- Some articles suggest that autoimmune response to dopamine-receptor is a possible mechanism in the pathogenesis of Parkinson's disease.[6]

Thus, Parkinson's disease which is a nervous system disorder seems to be affected by endocrine and immune system. This supports the 3X Hypothesis.

Hypertension

A powerful interaction between the autonomic and the immune systems plays

a prominent role in the initiation and maintenance of hypertension. Several studies have reported increased serum immunoglobulins (IgG and IgA) in hypertensive patients. On the other hand, in most hypertensive humans and animal models of hypertension, sympathetic nerve activity (SNA) is exaggerated.[7]

Thus, hypertension which is a physiological disease is affected by immune and nervous system. This supports the 3X Hypothesis.

Other Diseases

There is possibility that other physiological diseases can support this hypothesis. Connections between different physiological systems may be mentioned in ancient and traditional medical sciences, but the link between the three systems (nervous, immune, endocrine), their influence on each other that cause diseases, and the use of monitoring this connection to determine the cause of disease is not explained.

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Characteristic features of the clinical, genetic, hormonal and metabolic profile of girls with premature adrenarche

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Abstract: The analysis of the obtained results of hormonal and metabolic research in 33 girls with premature adrenarche was established high index NOMA values against the background of standard values of hormonal status. According to CYP-21 molecular genetic studies, a mutation of this gene was detected in 15.2% of girls. Of these, 60% had a mutation of the 7-Gen C 1994T gene and 40% had a mutation of the 4-Gen T999A gene and a heterozygous mutation of 2; 4-G655G; T999A. Mutation of the 21CYP gene correlates with high testosterone, 17-OH and androstendione, which indicates abnormal adrenal function.

Keywords: Premature adrenarche, congenital adrenal cortex dysfunction (CACD), Polycystic Ovarian Syndrome (PCOS), Puberty, Premature sexual development, Hyperandrogenia, Metabolic syndrome.

Premature adrenarche (PA) is an actual problem of children's endocrinology. This is due to the high prevalence of these conditions and the fact that these patients represent a risk group for the development of subsequent reproductive disorders, as well as diseases such as diabetes mellitus, coronary heart disease, dyslipidemia[10].

The mechanisms of development of premature adrenal glandular disease are currently the subject of discussion. Premature adrenarche is heterogeneous in its pathogenesis [8]. One of the reasons in girls may be the non-classical form of

congenital adrenal cortex dysfunction. The most common variant of inherent adrenal cortex dysfunction is 21-hydroxylase deficiency (NK21UN). Currently, there are no clear diagnostic hormonal criteria for NK210H, which leads to overdiagnosis of this form of the disease in adolescent girls and unjustified prescription of glucocorticoid therapy [6].

Studies by several authors have shown that puberty is characterised by a sharp increase in urine levels of 17-ketosteroids and levels of dihydrotestosterone, DGEA, and DGEA-S serum. Androstenedione, a

product of the beam zone, and 11-hydroxyandrostendone, a product of the mesh zone, do not increase during puberty. This increase is observed in girls and boys from 6 to 8 years of age, approximately 2 years before adolescence and youth (gonadarche) [2, 4].

Cortisol concentrations, production and excretion, do not change. Lack of regulatory data on adrenal steroidogenesis in children made it difficult to determine the endocrine effects of adrenal androgen in the past. Over the past 10 years, reference data on steroid hormones, their initial data and values after standard ACTH stimulation have been published, and have shown a significant wide range of norms, as well as gender differences [7].

In recent years, it has been shown that the development of premature adrenarche and puberty hyperandrogenism may be based on an increase in the functional activity of 17.20-liase in both the adrenal glands and ovaries. However, the question of what is the trigger mechanism for the activation of 17.20-liase remains unclear. It was shown in the experiment that such a factor might be insulin and insulin-like growth factor-1 [9].

In adult studies, it was found that 50% of women of reproductive age with the polycystic ovarian syndrome were found to be insulin resistant [1]. Studies on the child population are isolated. According to the literature, insulin resistance and compensatory hyperinsulinemia were found in 38% of teenage girls with hyperandrogenia who had a history of premature adrenarchy. It is assumed that these changes are associated with impaired insulin receptor phosphorylation [3, 11].

Given the high prevalence of carbohydrate metabolic disorders in patients with PA, it is of interest to study

the genes responsible for the formation of insulin resistance. The connection between insulin receptor-1 and insulin receptor-2 substrate polymorphism (IRS-1.2) and the development of insulin resistance in women with hyperandrogeny is shown. In addition, the data were obtained that the polymorphism of the INS VNTR gene is associated with low birth weight, postnatal catch-up and subsequent hyperinsulinemia in girls with hyperandrogenia [12].

Thus, the study of hormonal and metabolic changes in the child population is of interest, since their early diagnosis and correction will prevent the development of acute reproductive disorders, as well as diseases such as diabetes mellitus, obesity and CHD [5].

The objective of the study: To determine the hormonal and metabolic profile in girls with premature adrenal glands.

Materials and methods of research: 4000 sick children admitted to the polyclinic of RSSPMC Endocrinology in the period from 2012 to 2013 were examined, 57 of the girls showed signs of PA. During the detailed examination, 33 girls were diagnosed with various PA forms of pathogenesis.

The age gradation of the surveyed girls ranged from 6 to 9 years of age. The majority of adolescent girls were aged 6-7 years, or 57.6% (19 patients). 18.2 per cent of the girls were 5-6 years old. There was 24.2 per cent of patients aged 8-9 years.

Information about each patient, as well as data from archival materials was recorded in a specially designed questionnaire, which included the following indicators: anamnestic data, anthropometry data and sex formula, the results of the determination of hormones

in the blood, the results of instrumental examination, the results of the decision of bone age with the help of hand x-ray, the data of consultations of narrow specialists, as well as data on karyotyping.

The diagnosis of premature adrenaline was made on a clinical basis according to the following criteria:

- Variation of the pubic and axillary zones for up to eight years:
- absence of clitoromegaly;
- Breast development according to stage 1 of Tanner.

Patients with congenital adrenal cortex dysfunction, virilizing adrenal and ovarian tumors, and pituitary gland adenomas were excluded from the study group.

The control group consisted of 12 healthy girls aged 6-7 years.

The selection criteria for girls in the control group were:

- a) Absence of physical and sexual deviations.
- b) Lack of endocrine disorders and chronic somatic diseases.
- c) Absence of family history burden by tumours, hyperplastic processes of different localisation and endocrinopathies.

Assessment of physical and sexual development was carried out by analysing the physique and determining the formula of sexual development.

Hormonal (FSH, LH, testosterone, SSH, 17 -OH, DGEAS, androstenone, cortisol, TTG, prolactin, insulin), biochemical (glycaemia on an empty stomach, glucose tolerance test, lipid spectrum), statistical (calculation of the sample population, calculation of mean values, reliability of the study results) methods of study were used in this work.

Research results. In case of premature sexual development, the growth is significantly accelerated, and the bone age is higher than the passport age, which was noted in 45.3% of the surveyed girls. In other cases, there was isolated premature adrenaline, i.e. the bone age corresponded to the passport age.

The trend of increase in the pituitary and ovarian system and steroid hormones was revealed in all the interviewed girls with PA in the analysis of hormonal studies (Table 1).

Exciting data were obtained from the study of testosterone blood. Testosterone levels in the studied girls ranged from 0.2 to 2.7 nmol/l and averaged 2.38 ± 0.28 nmol/l, which is a reliably high value compared to control.

There is also a significant increase in FAI by 3.6 times and androstenone by 1.9 times, which indicates the presence of examined girls with PA hyperandrogenic.

Table 1
Data from hormonal studies of patients with premature adrenaline and control group

Indicators	The PA group. n=33	Control group n=12
FSH	5,3±2,8	4,1±3,2
LH	5,8± 2,3	6,9±2,2
Estradiol	161,6±43,7	154,4±69
Cortisol	337±160	282±124
Testosterone	2,38±0,28*	1±0,6
SHBG	37±17	68±26
FAI	5,1±1,3*	1,4±0,7

Note - * - reliability of data compared to the control group ($P < 0.05$)

Although clinical signs of hyperandrogenemia were observed in all patients of the study group, hormonal symptoms of hyperandrogenism (increase in testosterone levels) were revealed in 54.5% of cases. Therefore, the diagnostic significance of FAI indicators for the determination of functional addressable hyperandrogenic is of interest.

In the human body, the main structures capable of synthesising steroid hormones are the adrenal glands and ovaries. The common origin of the cells that form the adrenal cortex and the cells that make up the ovarian substance determines the similarity of the hormones synthesized in them and the identity of several enzymes involved in steroidogenesis. In the chain of transformation of prohormones into

androgens and their metabolites there are 4 consecutive fractions with increasing androgenic activity - dehydroepiandrosterone (DHEA), androstenedione, testosterone and dihydrotestosterone (DHT).

A study of level 17 of OA in girls with PA revealed adrenal secretion activity in the adrenal glands. Determination of androstendion concentration is less informative, as this hormone is secreted both in the adrenal glands and ovaries.

The analysis of the obtained results of the hormonal study revealed that the content of 17 OPs in the blood of girls with PA ranged from 2.9 to 11.6 nmol/l and averaged 3.6 ± 1.4 nmol/l, which was significantly ($p < 0.01$) higher than the corresponding figure in the control group (Table 2).

Table 2

Hormone levels of adrenal hormones in girls with PA

Indicators	The PA group. n=33	Control group n=12
DHEA	$6,5 \pm 3$	$3,7 \pm 0,6$
17OH	$3,6 \pm 1,4^*$	$1,3 \pm 0,8$
Androstendinone	$3,4 \pm 1,5^*$	$1,8 \pm 0,7$

Note - * - reliability of data compared to the control group ($P < 0.05$)

An almost 2-fold increase in the DVEA indicates premature sexual development. Acne and acne were observed in 54.5% of girls with PA, and hirsutism was observed in 34.8%.

Androstendion is a steroid hormone, which is the primary precursor of testosterone and estron. According to literature sources, an increased level of androstendion is observed, in particular, in hirsutism and virilization syndromes in women. Unlike androgens of the adrenal glands - dehydroepiandrosterone and its

sulfate - androstendion is secreted both by the adrenal bark and ovaries.

According to our studies, this indicator in girls with PA was almost 2 times higher than the control values (3.4 ± 1.5 vs 1.8 ± 0.7 ; $P < 0.05$).

Metabolic syndrome is now a significant burden on health care around the world. There is currently no consensus on the criteria for metabolic syndrome in children. Diagnosis of the metabolic syndrome and identification of patients at risk for preventive work are not less important.

Khaydarova Feruza Alimovna, Shariksieva Mukhlisa Abrolovna. Characteristic features of the clinical, genetic, hormonal and metabolic profile of girls with premature adrenarche

Hyperinsulinemia and obesity are often found in prepuberty and puberty in girls with a history of PA.

Clinical studies of children have shown that atherogenic risk factors can start in childhood. Thompson et al showed that CVD risk markers are already present in

overweight children as young as 9 years old.

According to the literature, insulin resistance was found in patients with a history of PA. In our study, we found a significantly high level of HOMA index in the PA group (Table 3).

Table 3

Insulin resistance in girls with PA and control group

Indicators	The PA group	Control group
Insulin	9,2±5,0	5,3±3,1
Glucose	4,6±0,3	4,7±0,4
HOMA index	3,1±1,2	1,5±0,6*

Note: * - reliability of data as compared to the control group ($P<0.05$)

Thus, in the group of girls with PA, the HOMA index value was 3.1 ± 1.2 , and in the control group 1.5 ± 0.6 ($p<0.01$)

Also recorded are high insulin levels, which exceeded the standard by 1.7 times.

Although the glucose values were almost the same.

The further stage of our work was the study of lipid metabolism in girls with PA and almost healthy girls (Table 4).

Table 4

Lipid metabolism rates for girls with PA and control group

Indicators	The PA group	Control group
Cholesterol	4,3±0,4	4,0±0,5
Triglycerides	0,68±0,28	0,65±0,21
HDL	1,3±0,4	1,5±0,5
LDL	2,6±0,4	2,5±0,3

As can be seen from the table, comparative data on lipid exchange did not reveal any positive difference between the indicators.

Thus, in the study of carbohydrate metabolism in girls with PA, an increase in the HOMA and insulin index was found against the background of healthy lipid metabolism.

According to the data obtained, the increase in production of steroids, as well as adrenal androgen, which have

moderate mineral-cortical properties, and their increase causes a delay of sodium and liquid in the body, which in turn leads to an increase in blood pressure, we studied the indices of dietary supplements, dietary supplements and average blood pressure (Table 5).

As can be seen from the data obtained, the increase in these indicators is observed, although not reliable. In the comparative analysis of dietary supplements and dietary supplements it

was increased by 1.1 times (108.6 ± 8.8 as the average value of dietary mmrt against 102.1 ± 6.8 mmrt and supplements. 59.6 ± 6.8 against 53.1 ± 5.5 mmrt), as well

Table 5

The blood pressure level in patients with PA and control group

Indicators	The PA group	Control group
SBP	$108,6 \pm 8,8$	$102,1 \pm 6,8$
DBP	$59,6 \pm 6,8$	$53,1 \pm 5,5$
Average blood pressure	$79,6 \pm 10,4$	$70,9 \pm 3,9$

A molecular genetic study of the CYP21 gene was performed on all PA girls. CYP21 mutations were established in 15.2% of cases. Mutation of the 7-gene C 1994T gene was found in 3 girls (60%), of whom heterogeneous in 2, and homogeneous in 1 girl with PA.

In 1 case, a heterozygous mutation of the 4 gene T999A was revealed, and in one girl with PA, a heterozygous mutation; 4 gene A/G655G; T999A.

The most frequent mutation of the CYP-21 gene was found at the age of 6 years in 60% of cases.

When studying the role of diagnostic markers 17-ON, DGEAS, and the determination of the mutation of 21 CSP in girls with PA, it was found that there

is a correlation between the detection of the mutation of 21 CSP and the increase in testosterone, 17 OH, and androstendinone (Table 6).

As can be seen from the table, girls with PA had high testosterone, 17-ON and androstendinone levels. Thus, the content of testosterone was 1.5 times higher in girls with PA without a CYP gene mutation (0.94 ± 0.4 vs. 1.42 ± 0.9). Indicators of 17-ON and androstendinone were 1.7 times (4.52 ± 2.3 vs. 2.6 ± 2.4 and 4.39 ± 2.83 vs. 2.52 ± 0.97 , respectively).

Thus, a mutation of the 21SYP gene was found in 15.2% of girls with PA, which correlates with high testosterone, 17-ON and androstendinone values, which indicates abnormal adrenal function.

Table 6

Age, BMI of testosterone, 17 OH and androstendinone depending on the presence of a mutation 21CYP

Indicators	Patients without a mutation 21CYP	Patients with identified heterozygous mutation 21CYP
Age	$6,7 \pm 1,3$	$4,8 \pm 0,7$
BMI	$17,4 \pm 2,4$	$18,1 \pm 3,3$
T	$0,94 \pm 0,4$	$1,42 \pm 0,9$
17OH	$2,6 \pm 2,4$	$4,52 \pm 2,3$
Androstendinone	$2,52 \pm 0,97$	$4,39 \pm 2,83$

Thus, the analysis of the hormonal results revealed that almost all girls with PA had normative values of FSH, LH,

estradiol, cartoon, testosterone, GSPH and ISA against the background of 2-fold increase of DGEA.

According to CYP-21 molecular genetic studies, a mutation of this gene was detected in 15.2% of girls. Of these, 60% had a mutation of the 7-Gen C 1994T gene, and 40% had a modification of the 4-Gen T999A gene, and a heterozygous mutation of 2; 4-G655G; T999A. In 15.2% of girls with PA, a mutation of the 21CYP gene is found, which correlates with high testosterone, 17-OH and androstendione levels, indicating abnormal adrenal glandular function.

The obtained results will contribute to the early identification of the causes of premature adrenal abnormalities, which makes it possible to rapid differentiated

correction of hormonal and metabolic disorders.

Conclusions:

1. When studying the hormonal and metabolic profile of girls with premature adrenaline, high values of the HOMA index were established against the background of normative values of hormonal status

2. Molecular genetic analysis of 15.2% revealed a confirmed congenital dysfunction of the adrenal cortex. Among girls with premature adrenal glandular dysfunction, the extra classical form of the CACD was found in 9.1% of cases, and the classical form in 6.1% of cases.

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