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Genetic Expression of *ALDH2* and *ADH1B* in Alcoholic Dependent Individuals in Iraqi Population

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Abstract

Alcohol addiction is a public health concern that affects communities all over the world, especially those with distinct genetic traits, such as the Iraqi community. This study investigates the genetic factors that contribute to alcohol dependence, focusing on the expression levels of Alcohol Dehydrogenase 1B (*ADH1B*) and Aldehyde Dehydrogenase 2 (*ALDH2*) genes in individuals from diverse regions of Iraq. A total of 250 blood samples were collected from males, ranging in age from 18 to 55, including 200 alcohol-dependent individuals and 50 samples as controls in the Iraqi population. The data showed a considerable increase in the expression level of the *ADH1B* (*P*-value < 0.0001; t= 6.447) among alcohol-dependent individuals compared to the control group. At the same time, the expression level of the *ALDH2* gene is significantly downregulated (*P*-value < 0.0001; t = 6.447) in alcohol-dependent individuals compared to the control. In alcohol dependence, *ADH1B* and *ALDH2* transcripts demonstrate different patterns that enable more efficient alcohol breakdown and protection against toxic aldehyde buildup. Alcohol detoxification roles of these enzymes demonstrate an extremely positive correlation through the result of r = 0.8347 with $p > 0.0001$. The protective mechanism between *ADH1B* and *ALDH2* becomes less effective when alcohol addiction continues, causing metabolic problems as well as disease development. The research confirms the essential metabolic interactions between *ADH1B* and *ALDH2* regarding alcohol dependence while showing the requirement for additional studies about their medical applications for prevention and therapy. Finally, the work reinforces the importance of genetic screening of these markers as possible tools for diagnosing individuals at risk for alcohol use disorders and establishing personalized therapy strategies to address the metabolic disturbances associated with alcohol dependency.

Keywords: Gene Expression, *ALDH2, ADH1B*, Alcohol dependent.

التعبير الجيني عن ALDH2 وADH1B في الأفراد المدمنين على الكحول في المجتمع العراقي

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الخلاصة:

يعتبر الادمان على الكحول مشكلة صحية عامة تؤثر على المجتمعات في جميع انحاء العالم ولاسيما في المجتمعات ذات الخصائص الوراثية الفريدة مثل المجتمع العراقي تهدف هذه الدراسة الى فهم العوامل الوراثية التي تسهم في الادمان على الكحول مع التركيز بشكل خاص على مستويات التعبير الجيني عن جينات انزيم لإنزيم الكحول *ديهيدروجينيز (ADH1B)* وإنزيم الألدهيد ديهيدروجينيز *(ALDH2)* لدى الأفراد المدمنين على الكحول في مناطق مختلفة من ولتحقيث هذا الهدف تم جمع 250 عينة دم من الذكور الذين تتراوح اعمارهم بين 18 و 55 عاما و كان عدد الاشخاص المدمنين على الكحول 200 و عدد الاشخاص الاصحاء 50. اظهرت النتائج زيادة كبيرة في تعبير انزيم الكحول ديهايدروجينيز *ADH1B*(*P*–value < 0.0001; t= 6.447) بين الافراد المدمنين على مقارنة بمجموعه الاشخاص الاصحاء بينما لوحظ انخفاضا ملحوضا في التعبير الجيني لانزيم وإنزيم الألدهيد ديهيدروجينيز (*P*–value < 0.0001; t = 6.447) *(ALDH2)* في حالة الاعتماد على الكحول، تُظهر جينات *ADH1B* و*ALDH2* أنماط تعبير مختلفة تسهم في تعزيز تفكيك الكحول بشكل أكثر كفاءة وتوفير الحماية ضد تراكم الألدهيد السام. تُظهر أدوار هذه الإنزيمات في إزالة السموم من الكحول ارتباطًا إيجابيًا قويًا، حيث بلغت قيمة معامل الارتباط (r = 0.8347, $p > 0.0001$). ومع ذلك، يصبح هذا التأثير الوقائي أقل فاعلية مع استمرار إدمان الكحول، مما يؤدي إلى اضطرابات في التمثيل الغذائي وتطور الأمراض. تؤكد هذه الدراسة على التفاعل الأيضي الأساسي بين *ADH1B* و*ALDH2* فيما يتعلق بالاعتماد على الكحول، مع التأكيد على الحاجة إلى مزيد من الأبحاث حول تطبيقاتهما الطبية للوقاية والعلاج. وأخيرًا، تسلط الدراسة الضوء على أهمية الفحص الجيني لهذه العلامات كأدوات محتملة لتشخيص الأفراد المعرضين لخطر اضطرابات استخدام الكحول، وتطوير استراتيجيات علاجية مخصصة لمعالجة الاضطرابات الأيضية المرتبطة بالإدمان على الكحول.

Introduction

Alcohol impairs mental functioning in stages, beginning with judgment and reasoning and progressively impacting more basic functions as consumption increases. Initially, alcohol diminishes judgment and reasoning, followed by impairments in motor skills and reaction times. At blood alcohol concentrations (BAC) of 0.06-0.09, coordination is significantly compromised, rendering activities such as driving hazardous. Moreover, alcohol is strongly associated with heightened aggression and violent behavior, playing a role in approximately half of all violent crimes and sexual assaults worldwide. It is also a significant contributor to suicides, second only to depression [1,2]. Other research shows that individuals with a family history of alcohol abuse were more likely to develop similar problems, with twin and adoption studies supporting the presence of a genetic component [3]. Genetic research identified specific gene polymorphisms, particularly those related to alcohol metabolism, that influenced an individual's susceptibility to alcohol dependence and replicated [4,5].

Alcohol Dehydrogenase (ADH), a crucial enzyme in human alcohol metabolism, was found to vary in activity as people aged. Research indicates that hepatic cytosolic ADH activity decreases as people age. This decrease in ADH activity most likely led to older persons' greater vulnerability to the harmful effects of alcohol [6]. After alcohol consumption, approximately 20% was absorbed by the stomach, while the intestines absorbed the remainder. The liver primarily metabolizes the alcohol, converting it into fatty acids and other byproducts [7]. Only a tiny portion of the alcohol was excreted through breath, urine, or sweat. As alcohol was metabolized, it could result in the accumulation of triglycerides in the liver, leading to fatty liver disease and, over time, cirrhosis [8]. *ALDH2* genes have been identified as significant epigenetic markers linked to problematic drinking and alcohol use disorder (AUD), with risk variations in these genes being associated with a variety of psychiatric diseases altered by stress [9]. Genetic studies revealed that specific individuals had a natural predisposition to alcohol dependence due to variations in genes responsible for

alcohol metabolism [10]. The central genes involved were alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH). Variants such as *ADH1B-2*, *ADH1B-3, ADH1C-1*, and *ALDH2-2* were associated with lower rates of alcohol dependence, as they influenced the breakdown of alcohol and the accumulation of acetaldehyde, which could produce unpleasant effects and reduce alcohol consumption [11]. This genetic variation was common among East Asians, with about 40% carrying it, but was rare in Europeans. This genetic trait helped limit alcohol intake and reduced the risk of alcohol dependence [12,13]. Association between genetic polymorphism of ADH3 exon 8 and ADH2 exon 9 genes and specific enzymes with Alcoholism in Iraq. While studies have been conducted on the Alcohol Dehydrogenase genotypes, specifically *ADH2* and *ADH3*, in the Iraqi population [14], no research has been conducted on the gene expression of ADH in this group. As a result, this study sought to fill this gap by studying the gene expression of *ALDH2* and *ADH1B* in alcohol-dependent individuals from diverse regions of Iraq. This study sheds light on the molecular mechanisms of alcohol dependence in the Iraqi population.

Subjects, materials, and methods

Subjects

This study aimed to investigate the gene expression of alcohol metabolism by examining the responsible enzymes. The sample included alcohol-dependent individuals aged 18 to 55 years from three regions of Iraq. A total of 250 samples were intentionally categorized into three groups based on an analysis of their housing environments in relation to their place of residence. The groups included 50 samples from alcohol-dependent individuals in southern Iraq (specifically from Basra, Nasiriya, and A 'Amara), 50 samples from alcohol-dependent individuals in central Iraq (including Najaf, Karbala, Samawah, and Diwaniyah), 50 samples from alcohol-dependent individuals in Baghdad, and 50 samples from alcohol-dependent individuals in northern Iraq (comprising Mosul, Salahuddin, and Diyala). Additionally, 50 samples were included as a control group. All alcohol-dependent and controlled samples of these individuals who volunteered to participate in the study provided informed written consent. Between January and August 2024, research was conducted at Al-Nahrain University's Forensic DNA Centre and Training. The Medical City Hospital Ethics Committee and the University of Baghdad's Committee for Postgraduate Studies (CSEC/1124/0105) approved the experiment.

Exclusion Criteria

Men who consumed alcohol inconsistently or intermittently, as well as those who were both alcoholics and drug addicts, were excluded from the study. Additionally, men with chronic diseases such as cardiovascular disease, diabetes mellitus, kidney failure, or hypertension were omitted.

Sample Collection

Peripheral blood (PB; 4 mL) was collected from each participant, and 0.3 mL of PB was used for gene expression analysis.

The RNA quantification and qPCR

The RNA was extracted according to the protocol of the TRIzol reagent (ELK Biotechnology, China).

The quantification of RNA was carried out using a Quantus Fluorometer. For this process, 2 µL of RNA was combined with 198 µL of diluted Quantifluor Dye. The RNA concentration values were recorded after incubating the mixture at room temperature in the dark for 5 minutes. The qPCR reaction is a two-step process that involves converting RNA into complementary DNA (cDNA) in the first reaction, followed by a separate polymerase chain

reaction (PCR) to amplify the cDNA in the second reaction. The cDNA reaction was prepared as follows: a total volume of 20 µL, consisting of 10 µL of the reaction mixture, 1 µL of the MMLV-RT enzyme, 500 ng of RNA, 1 µL of the oligo primer, and the final volume was completed with nuclease-free water.

The reaction program is as follows: an annealing step at 25°C for 5 minutes, an extension step at 42°C for 60 minutes, enzyme inactivation at 70°C for 15 minutes, and a hold step at 4°C for 10 minutes.

For the second reaction, the qPCR calculation was done with the following master mix components: 10 µL of Luna® Universal qPCR, 0.5 µL each of forward and reverse primers as shown in Table 1, 6 µL of nuclease-free water, and 3 µL of cDNA, making a total volume of 20 µL.

The qPCR program began with an initial denaturation at 95°C for 1 minute, followed by 45 cycles of denaturation at 95°C for 15 seconds and annealing at 58-63°C for 30 seconds. At the end of the reaction, a melt curve analysis was done to ensure that the amplification was specific. The 2^-ΔΔCT Livak method was used for data analysis.

Table 1: Primers used in this study.

Primer Name	Primer Sequence	Tm	References
RPL27-F	ATCGCCAAGAGATCAAAGATAA	58	[15]
RPL27-R	TCTGAAGACATCCTTATTGACG		
ADH1B-F	GGGAAGCCCATTCACCACTT	63	Designed in this study
ADH1B-R	TAGAGCCTGGGGTGACCTTG		
ALDH2-F	GGCACTGTGTGGGTCAACT	63	Designed in this study
ALDH2-R	GAGGGAGGAAGCTTGCATGA		

Statistical analysis

Statistical evaluation was done with Prism-Graph Pad. An unpaired *t*-test was used to compare the two sample groups, and a *P*-value of less than 0.05 was judged statistically significant, resulting in the rejection of the null hypothesis. The Pearson correlation coefficient test was used to calculate the correlation between the gene expression of *ALDH2* and *ADH1B*.

Results

The findings showed that the expression level of *ALDH2* in alcohol-dependent individuals was significantly downregulated and the fold change of around 0.5 with (p-value < 0.0001; t = 6.447) compared to the control sample, which showed a fold change of about 1.0, and serving as a baseline for comparisons. as shown in Figure 1.

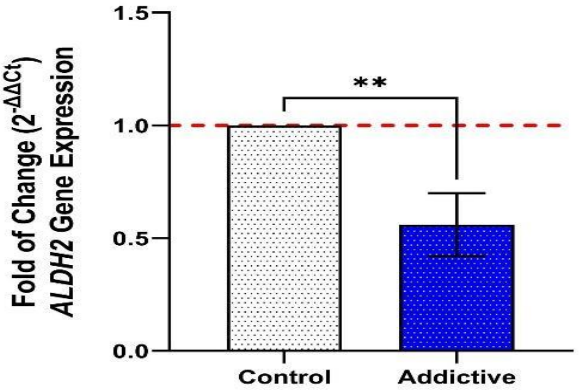

Figure 1: Real-time PCR analysis in alcohol-dependent individuals representing the expression levels of an *ALDH2* gene. The figure shows a significant decrease in expression levels of *ALDH2* in alcohol-dependent individuals compared to the controls. *t*-test, N=250, *P*<0.0001.

The expression level of the *ADH1B* gene revealed significant upregulation (*P*-value < 0.0001; t = 6.447) with a nearly 30-fold change in alcohol-dependent individuals compared to the control sample, which showed a fold change of about 2.73, as shown in Figure 2. The fold change follows the method $2^{-\Delta\Delta Ct,}$ where the $\Delta\Delta Ct_{(patients)}=\Delta Ct_{(patients)}- \Delta Ct_{(Control)}$.

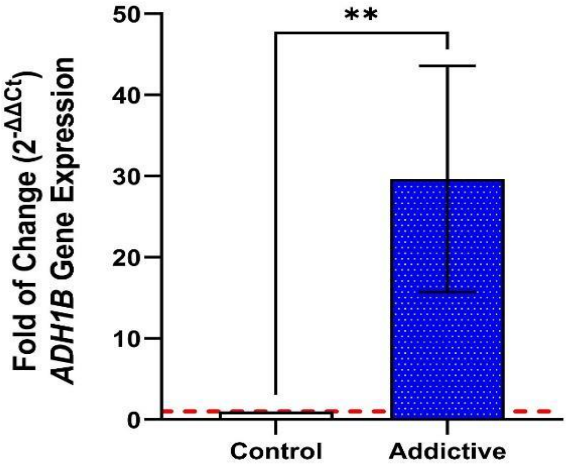

Figure 2: Real-time PCR analysis in alcohol-dependent individuals representing the expression levels of an *ADH1B* gene. The figure shows significantly upregulated levels of *ADH1B* expression in the alcohol-dependent individuals compared to the control. *t*-test, N=250, *P*<0.0001.

The results of the correlation between the gene expression of *ALDH2* and *ADH1B* in alcohol-dependent individuals, using Pearson correlation, showed a substantial and significant positive relationship between these two variables at (r (250) = .835, $p < .001$), as shown in Table 2. A strong positive correlation exists between the genes because the Pearson correlation coefficient equals 0.8347, which indicates that enhanced gene expression in one element matches higher expression in the other. One gene's expression variation can be attributed to nearly 70% of the expression level of the other gene based on the coefficient of determination ($r^2 = 0.6967$). The *P*-value (1.913e-12) demonstrates extremely strong evidence of statistical importance because the correlation occurs infrequently by chance. This correlation strength matches the magnitude of covariance, which amounts to 4496.702. The increase in data points to 44 provides stronger reliability to the correlation analysis. The

correlation statistics of 9.822 demonstrate knowledge of the high statistical significance of the relationship.

Table 2: Pearson correlation results from the *ALDH2* and *ADH1B* gene expression.

Parameter	Value
Pearson correlation coefficient (r)	0.8347
r^2	0.6967
P-value	1.913e-12
Covariance	4496.702
Sample size (n)	250
Statistic	9.822

Discussion

The results of this study indicate significant alterations in the gene expression of *ALDH2* and *ADH1B* in alcohol-dependent individuals, highlighting their potential importance in alcohol metabolism and dependency. Samples were collected from different Iraqi regions; choosing samples from the various areas of Iraq helps capture the genetic and environmental diversity that may impact alcohol metabolism and dependence. This strategy ensures that the study reflects a more comprehensive picture of the population, acknowledging regional variations that could influence gene expression and the overall findings.

The *ADH1B* expression increased significantly in alcohol-dependent individuals, which showed a fold change of 30, contrary to 2.37 in control samples, indicating that overexpression of this gene can accelerate acetaldehyde production. The findings also showed that alcohol-dependent individuals had significantly lower levels of *ALDH2* expression than the control group, which was approximately 50%. This is because *ALDH2* converts acetaldehyde, a toxic byproduct of alcohol metabolism, to acetate [16,17,18].

The higher levels of *ADH1B* expression indicate faster ethanol metabolism. Nonetheless, acetaldehyde synthesis may exceed detoxification capacity, resulting in a dangerous accumulation. Since *ADH1B* promotes the oxidation of ethanol into acetaldehyde, a toxic result of alcohol metabolism [19,20]. Meanwhile, *ADH1B* gene expression in other research shows decreased expression levels in different types of cancer [21, 22]. The decreased expression of *ADH1B* in metabolism can potentially generate inflammatory tumor conditions, which lead to cancer. This is opposite to the increased *ADH1B* expression, which occurs with alcohol dependence. The MAPK signaling pathway becomes inactive after *ADH1B* overexpression, which leads to tumor suppression and prevents tumor proliferation, invasion, and migration [23].

The observed downregulation of *ALDH2*, which is commonly associated with alcoholism due to its function in acetaldehyde detoxification, could still be a compensatory mechanism that fails over time. In alcohol-dependent individuals, the body may attempt to manage acetaldehyde levels at first, but continuous downregulation of *ALDH2* results in insufficient acetaldehyde clearance. This causes toxic buildup, increasing the damaging effects of alcohol [24]. As the expression of *ALDH2* decreases, the body's ability to convert acetaldehyde to the less harmful acetate is compromised, leading to its accumulation[25,26]. This buildup triggers oxidative stress and sets off a cascade of damaging effects on cellular structures and organ function. In addition, it causes toxic consequences such as headaches, nausea, and an increased risk of long-term tissue damage, notably in the liver, cellular damage, and inflammation [27]. Acetaldehyde's continuous presence may enhance addictive behaviors,

probably due to the disruption of neurotransmitters in the brain. Research indicates that high levels of acetaldehyde impact dopamine pathways, which reinforces addictive behavior and sustains alcohol use despite negative consequences[28]. This produces an endless cycle in which alcohol intake persists despite its negative consequences, fueled by both addiction and the body's decreased ability to handle acetaldehyde poisoning [29,30]. This led to the current medical treatment, which is converting alcohol to acetaldehyde or acetate, like naltrexone and other drugs that help in alcohol treatment [31,32]. As a result, individuals with *ALDH2* downregulation build acetaldehyde in their bodies after consuming alcohol, which is a similar feature to *LUAD* and *CRC* cancers, as poorly expressed *ALDH2* fuels toxic aldehyde buildup and inflammatory conditions and raises tumorigenic potential [33,34]. The enzyme regulates critical metabolic intermediates to control immune responses and stemness pathways. In alcohol-dependent individuals, its deficiency results in impaired mitochondrial fatty acid oxidation and reduced energy expenditure while increasing lipid accumulation [35]. Research into *ALDH2* activators has shown clinical success across various cancer diseases and metabolic illnesses, which demonstrates that targeting *ALDH2* represents a promising method to control illness development, improve patient medical results, and decrease inflammatory processes [36,37].

Alcohol-dependent individuals have *ADH1B* overexpression, which leads to increased acetaldehyde synthesis; here comes the role of *ALDH2* that converts acetaldehyde to acetate, but the reduced expression of ALDH2 leads to the accumulation of acetaldehyde and not only contributes to the deleterious consequences of alcohol, but it also encourages additional alcohol consumption, hence prolonging addiction. These findings suggest that genetic factors, such as *ADH1B* overexpression and *ALDH2* downregulation, play a crucial role in the development of alcohol-related disorders. *ADH1B* and *ALDH2* transcript levels were linked with regulating metabolism, cell cycle, DNA repair, and cancer-associated pathways [38].

Research shows that alcohol dependence creates intricate relationships between the *ADH1B* and *ALDH2* genetic factors. The enzymes demonstrate high levels of coordinated activity based on their positive correlation of 0.8347, which indicates they adjust together when exposed to long-term alcohol use. The data shows increased activity of the *ADH1B* gene because cells adapt their responses to elevated ethanol concentrations. The simultaneous decrease of the detoxifying enzyme *ALDH2* results in the buildup of toxic byproducts because of its fundamental role in clearing acetaldehyde. The short-term decrease of *ALDH2* expression seems beneficial, but proves unsuccessful as alcohol consumption persists. This expression failure creates an environment with elevated toxicity while simultaneously promoting inflammatory reactions that increase the chance of pathophysiological deterioration. The research results demonstrate a coordinated expression pattern between *ADH1B* and *ALDH2*. However, the diminished *ALDH2* function indicates an unfavorable impact on its protective capacity against alcohol-induced tissue damage.

Understanding the genetic interplay between *ADH1B* and *ALDH2* not only sheds light on the pathophysiology of alcohol dependence but also opens the door to targeted genetic or pharmacological interventions that could improve treatment outcomes [39].

This study has several limitations. The study uses 250 male participants based on their regional categorization but excludes female participants, limiting potential generalization beyond Iraqi males. A cross-sectional study methodology restricts researchers from noting temporal changes or adjusting for changing lifestyle variables. Multiple complicated aspects, such as nutrition, health conditions, and genetic differences, prove difficult to manage, and their effect on enzyme expression remains unclear. The dependent nature of alcohol use information from participants introduces possible reporting bias along with potential matching differences between the small control sample and alcohol-dependent groups [40].

Conclusion

Finally, this study showed considerable excessive activity of both *ADH1B* and *ALDH2* in alcohol-dependent individuals, highlighting a complicated genetic interaction that has a significant impact on alcohol metabolism. *ADH1B* promotes the conversion of ethanol into the risky byproduct acetaldehyde, but *ALDH2*, despite its high activity, is unable to eliminate the accumulating acetaldehyde adequately. This continuous discrepancy causes high acetaldehyde levels, which increase alcohol's adverse effects and prolong addicted tendencies. Chronic alcohol exposure seems to regulate both *ADH1B* and *ALDH2* since alcohol-dependent patients present a strong positive correlation (r=0.8347) between these enzymes. The findings highlight the need to incorporate both genes when assessing genetic susceptibility to alcohol dependency, as well as indicate that tailored treatment techniques targeting these metabolic abnormalities may be required for successfully controlling alcohol use disorders. More research is needed to establish the potential uses of these genetic markers in therapy, especially in Iraqi populations.

Conflict of interest

I pledge that I have no conflict of interest with other researchers.

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