

Comparing Mizaj (temperament) in type 1 diabetes mellitus and healthy controls: A case–control study

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Background: Diabetes mellitus (DM), named *Ziabites* in Persian medicine (PM), was categorized as hot or cold *Ziabites* according to the Mizaj of patients. This study aimed to compare the Mizaj of patients with newly diagnosed type 1 DM (T1DM) with chronic cases and healthy children. **Materials and Methods:** In a case–control study, three groups including chronic T1DM patients ($n = 31$), newly diagnosed T1DM patients ($n = 37$), and healthy children as the control group ($n = 80$) were recruited. Mojahedi Mizaj Questionnaire was used to measure two subscales, hot/cold and wet/dry, of Mizaj for participants. The mean scores of the Mizaj subscales were compared between the groups. Cutoff values were determined using receiver operating characteristic analysis, and the corresponding odds ratio (OR) for each subscale was identified. **Results:** Overall 148 participants, with a mean age of 10.0 ± 6.2 years, were enrolled in the study. Analysis showed that the mean total heat and total dryness scores were significantly higher in new T1DM than that of chronic patients and healthy children (19.59 ± 1.7 vs. 16.6 ± 2.1 and 18.17 ± 1.9 , $P < 0.001$ for hot/cold and 4.70 ± 1.0 vs. 4.09 ± 0.9 and 4.31 ± 0.8 , $P = 0.02$ for wet/dry). “Extra heat” based on the cutoff value of >18.5 was found to be a risk factor for T1DM (OR = 3.62, 95% confidence interval = 1.52–8.63). **Conclusion:** New T1DM patients have higher frequency of hot and dry Mizaj, which is consistent with the concept of hot *Ziabites* in PM. Most importantly, we found that “extra heat” in children can be considered as a risk factor for T1DM.

Key words: Mizaj, Persian medicine, temperament, type 1 diabetes mellitus, *Ziabites*

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INTRODUCTION

Diabetes mellitus (DM) refers to a group of metabolic disorders that are associated with an impairment in plasma glucose regulation.^[1] Recently, diabetes has been linked to impairments in temperature regulation during exposure to thermal stress. The topic of diabetes and heat exposure remains a new area of investigation.^[2]

The School of Persian Medicine (PM) was established on the basic concept of Mizaj (temperament).^[3-7] In the context of this concept, each person has a unique

characteristic named Mizaj which is recognized by his or her morphological, physiological, and psychological features.^[8,9] According to the PM, a person is considered to be in a healthy state when his or her Mizaj keeps its balance and most of the diseases occur when the Mizaj becomes imbalanced (Sue Mizaj).^[5,10] Mizaj is imagined as a two-dimensional spectrum of hotness to coldness and wetness to dryness. According to this concept, each individual is susceptible to certain diseases related to his or her Mizaj and therefore different individuals may need different treatments and lifestyle recommendations.^[10,11] In other words, in the PM, the Mizaj acts as a road map for the maintenance of an individual’s health.^[5,7,11]

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The term *Ziabites* was used to describe diabetes, in the PM. This disorder was categorized as a subgroup of imbalanced Mizaj diseases named Sue-Mizaj and divided into two main types, hot and cold *Ziabites*. Etiologically, hot and cold *Ziabites* results from endo- or exogenous extra heat and extra coldness, in whole body or some organs such as kidneys and liver, respectively. Therefore, hot *Ziabites* patients have an impaired capacity to tolerate heat, contrary to the cold *Ziabites*.^[12-15] However, there are some disagreements among traditional physicians in pertaining hot or cold *Ziabites* to different types of diabetes in classic medicine.^[16,17] Thus, it remains to indicate whether type 1 diabetes are related to hot or cold *Ziabites*. This study aimed to measure Mizaj in two samples (new diagnosed and chronic) of confirmed diabetic children and indicates how their Mizaj differs from healthy children.

MATERIALS AND METHODS

Design and participants

This case-control study was carried out in Isfahan, Iran, in 2015. Three groups of participants included to the study. The first and second groups were newly diagnosed T1DM (new cases) and chronic T1DM (chronic cases) children from Isfahan Endocrine and Metabolism Research Center as case groups. Third group were nondiabetic students of Isfahan Schools as Control. New cases and controls were age and sex matched, whereas chronic cases were not age matched because of the duration of diabetes. The participants or their parents voluntarily agreed to take part in the study by giving their informed consent. Children filled the questionnaire themselves, or the parents filled for their children in case of <8 years old. The participants were assured that their information would remain confidential. In control group, the volunteers with a history of chronic diseases or sustained drug use at the time of the study were excluded from the study. The patients with a history of any disease except diabetes or use of any drugs except insulin were also excluded. Patients with a history of duration of diabetes <1 year were enrolled in the new T1DM group and more than 1 year were enrolled in the chronic T1DM group.

Questionnaire

The Mojahedi Mizaj Questionnaire (MMQ) was used to measure the Mizaj of participants. This is a brief self-reported questionnaire that designed for indicating Mizaj. The questionnaire contains ten questions. Each question is rated on a three-point scale ranging from 1 to 3. Of these, eight questions are related to hot/cold and two are related to wet/dry subscales. Question phrase is presented in the questionnaire in Appendix 1. According to this scale, each respondent finally has two scores: one for hot/cold subscale (a total score ranging from 8 to 24)

and one for wet/dry subscale (a total score ranging from 2 to 6). The best cutoff point for hot Mizaj is ≥ 19 and for cold Mizaj is ≤ 14 on hot/cold subscale. Similarly, the best cutoff point for dry Mizaj is ≥ 5 and for wet Mizaj is ≤ 3 on wet/dry subscale. The psychometric properties of the MMQ are well documented.^[4]

Statistical analysis

Continues and categorical data were represented as mean \pm standard deviation and frequency (percentage), respectively. Normality of continuous data was evaluated using Kolmogorov-Smirnov and Q-Q plot. Receiver operating characteristic (ROC) curve analysis was used for determining the predictive role of Mizaj scores for differentiating the newly diagnosed diabetic patients from healthy participants. Then, the area under the curve (AUC) was calculated, and the best cutoff values with highest sensitivity and specificity corresponding to the scores of Mizaj were determined.

In addition, we used simple binary logistic regression analysis to evaluate the relationships between the determined best cutoff values of Mizaj scores and the risk of T1DM onset of T1DM. Odds ratios (ORs) and 95% confidence intervals (CIs) for OR were calculated.

$P < 0.05$ was considered statistically significant. Statistical analyses were performed by SPSS version 16 (version 16, SPSS Inc., Chicago, IL, USA).

Ethics

This study was a part of the PhD thesis (ID No. 186). Ethical approval was obtained from the Ethics committee of Shahid Beheshti University of Medical Sciences (ID No. IR.SBMU.RETECH.REC.1395.625).

RESULTS

One hundred and forty-eight participants were enrolled in the study. Of these, 37 individuals were patients with new T1DM, 31 individuals were patients with chronic T1DM, and the remaining 80 were healthy controls. The mean age of the participants was 10.0 ± 6.2 years. There were no significant age ($P = 0.10$) or gender ($P = 0.15$) differences between groups, but the age of chronic cases was significantly higher than others ($P < 0.001$) because of the duration of disease. The mean duration of DM was 10.72 ± 6.5 months in new T1DM and 91.5 ± 70.0 months in chronic T1DM patients. The demographic characteristics of the samples and their Mizaj question scores are shown in Table 1.

The mean of total heat scores was significantly higher in new cases than chronic patients and healthy children

Table 1: Demographic characteristic of the study samples and their question results, in three groups

	Chronic cases (n=31), n (%)	New cases (n=37), n (%)	Control (n=80), n (%)	P*
Demographic characteristic				
Age groups (years), mean (SD)	17.5 (9.9)	9.9 (7.7)	8.43 (1.6)	0.001
Gender				
Male	11	19	30	0.15
Female	20	18	50	
Duration of DM (month), mean (SD)	91.5 (70.0)	10.72 (6.5)	-	-
Hot/cold subscale questions				
Hand temperature (Q1)				
Cold	10 (32.3)	7 (18.9)	9 (11.2)	0.004
Norm	14 (45.2)	12 (32.4)	50 (62.5)	
Hot	7 (22.6)	18 (48.6)	21 (26.2)	
Thermal impressibility (Q2)				
Cold	6 (19.4)	2 (5.4)	6 (7.5)	<0.001
Norm	18 (58.1)	2 (5.4)	27 (33.8)	
Hot	7 (22.6)	33 (89.2)	47 (58.8)	
Irritability (Q3)				
Slow	2 (6.5)	3 (8.1)	9 (11.2)	0.035
Norm	9 (29.0)	3 (8.1)	27 (33.8)	
Rapid	20 (64.5)	31 (83.8)	44 (55.0)	
Hand size (Q4)				
Small	5 (16.7)	6 (16.2)	9 (11.2)	0.003
Norm	22 (73.3)	21 (56.8)	68 (85.0)	
Large	3 (10.0)	10 (27.0)	3 (3.8)	
Speech rapidity (Q5)				
Slow	7 (22.6)	3 (8.1)	5 (6.2)	0.039
Norm	16 (51.6)	16 (43.2)	48 (60.0)	
Rapid	8 (25.8)	18 (48.6)	27 (33.8)	
Food impressibility (Q6)				
Cold	8 (27.6)	3 (9.4)	14 (17.5)	<0.001
Norm	17 (58.6)	16 (50.0)	60 (75.0)	
Hot	4 (13.8)	13 (40.6)	6 (7.5)	
Movement (Q7)				
Slow	5 (16.1)	4 (10.8)	9 (11.4)	0.046
Norm	18 (58.1)	15 (40.5)	24 (30.4)	
Rapid	8 (25.8)	18 (48.6)	46 (58.2)	
Voice power (Q8)				
Low	5 (16.1)	2 (5.4)	3 (3.8)	0.163
Norm	13 (41.9)	13 (35.1)	33 (41.2)	
High	13 (41.9)	22 (59.5)	44 (55.0)	
Wet/dry subscale questions				
Obesity index (Q9)				
Fatty	5 (16.1)	1 (2.7)	4 (5.1)	0.025
Norm	20 (64.5)	17 (45.9)	40 (50.6)	
Thin	6 (19.4)	19 (51.4)	35 (44.3)	
Skin dryness (Q10)				
Soft	8 (25.8)	12 (32.4)	23 (28.8)	0.002
Norm	13 (41.9)	5 (13.5)	40 (50.0)	
Coarse	10 (32.3)	20 (54.1)	17 (21.2)	

*Comparison among groups was assessed using one-way ANOVA for quantitative and Chi-square test for categorical data. SD=Standard deviation

(19.59 ± 1.7 vs. 16.6 ± 2.1 and 18.17 ± 1.9, $P < 0.001$). Furthermore, the mean of total dryness scores was significantly higher in new T1DM than chronic patients and healthy children (4.70 ± 1.0 vs. 4.09 ± 0.9 and 4.31 ± 0.8, $P = 0.02$, respectively).

The majority of the new T1DM patients have hot and dry Mizaj (75.7% and 56.8%, respectively); they were significantly hotter ($P < 0.0001$) and dryer ($P = 0.04$) than controls. On the contrary, chronic T1DM were significantly colder (16.6 ± 2.1 vs. 18.17 ± 1.9, $P = 0.001$) than controls. Comparison of

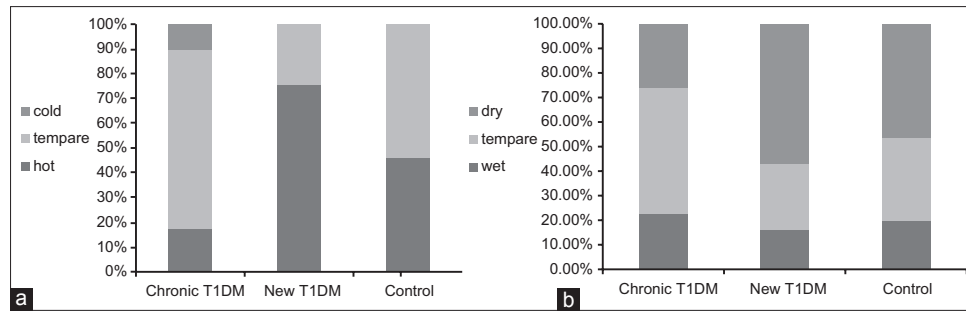


Figure 1: Mizaj distribution of participants between three groups; (a) hot/cold scale, (b) wet/dry scale

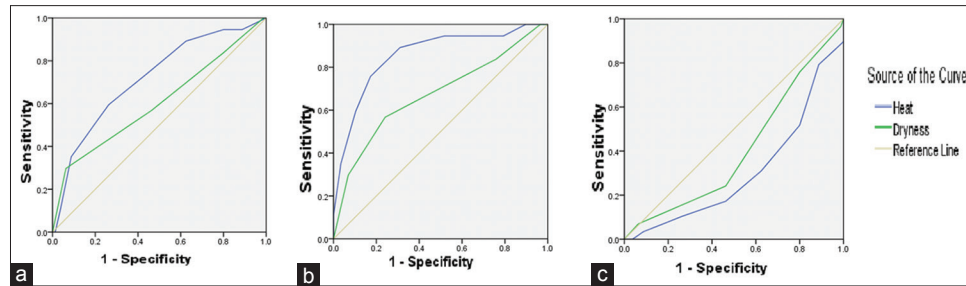


Figure 2: The area under curve (a): New diabetic from healthy, (b): New diabetic from chronic, (c): Chronic diabetic from healthy; based on heat and dryness scores

the model of Mizaj contribution (percentage) among three groups is presented in Figure 1.

Area under the ROC curve (AUC) was evaluated for hot/cold and wet/dry subscales between groups pair wisely [Figure 2].

The best cutoff values for the scores of subscales and their odds ratios were presented in Table 2. According to the results the “Extra heat” (cutoff >18.5) was found to be correlated with new onset of T1DM (OR = 3.61, 95% CI = 1.51–0.63) [Table 2].

DISCUSSION

Ziabites is considered a dystemperamental (sue Mizaj) disease in PM, resulting from disturbance of heat balance equation. *Ziabites* is also divided into two main types: hot and cold *Ziabites*.

The results of the present study showed that the Mizaj of children with new T1DM was significantly hotter and dryer than control group, and the Mizaj of children with chronic T1DM was significantly colder than control group as measured by the MMQ.

Our regression analysis showed that the risk of new T1DM in healthy hot Mizaj children increased. Furthermore, the analysis showed a greater association between dry Mizaj and new cases; it is considered as a DM side effect not as a predictor for T1DM onset.

Cold Mizaj in chronic T1DM patients versus new cases and controls could be due to the several interfering factors such as chronicity of DM and BS levels, diabetic complications, or the effect of drugs (insulin).

Because the MMQ assessed some constitutional factors that usually are not temporary or expected to be suffered during short time of new cases in our participants, “extra heat” in children may be considered as a risk factor for T1DM. More (prospective) studies are needed to comprehensively reveal temperamental risk factors for T1DM.

The cutoff point of heat score in our study (>18.5) was similar and near to findings by Mojahedi *et al.*'s study (≥ 19).^[5]

Significant differences in heat and dryness scores between long-lasting and new cases may be due to treatment effects or perhaps insulin itself or duration of DM and appearance of subclinical side effects. These findings indicate that severe or chronic diseases can affect the constitutional factors of Mizaj.

The findings of this study indicated that 75% of new T1DM children had hot Mizaj; this is in agreement with traditional documents which believe that hot *Ziabites* is more frequent and cold *Ziabites* is rare.^[8,12,14] Furthermore, our analysis showed that the percent of dryness of new cases are more than controls. It could be considered as DM side effect or a predictor for T1DM onset, more survey needs to prove one of them. Similar to the incidence rate of hot *Ziabites* in new T1DM children in our study, type 1A involves about

Table 2: Cutoff points and odds ratio for significant area under the curves between pair wise groups (binary logistic regression)

Variables	AUC (95% CI)	P	Cutoff point	Sensitivity	Specificity	OR (95% CI)
New cases versus controls						
Hotness	0.71 (0.61–0.81)	<0.001	18.5	0.75	0.46	3.61 (1.51–0.63)
Dryness	0.60 (0.48–0.72)	0.071	4.5	0.56	0.46	1.52 (0.69–3.34)
Chronic cases versus controls						
Hotness	0.30 (0.19–0.41)	0.002	NA	NA	NA	NA
Dryness	0.40 (0.28–0.52)	0.139	NA	NA	NA	NA
New cases versus chronic cases						
Hotness	0.85 (0.76–95)	<0.001	17.5	0.89	0.31	18.33 (4.98–67.41)
Dryness	0.67 (0.54–0.80)	0.017	4.5	0.56	0.24	3.77 (1.34–10.61)

NA=Not applicable; CI=Confidence interval; OR=Odds ratio; AUC=Area under the curve

80% of T1DM children.^[1] It needs more investigation to know whether type 1A of DM is related to hot *Ziabites*. Recently, we reported similar findings, showing that using PM treatments on hot *Ziabites* led to extended honeymoon period in a type 1 diabetic boy.^[18] Other studies revealed that almost 70% of recommended medicinal herbs for hot or cold types of *Ziabites* in PM references, have antidiabetic effects.^[19,20] In spite of PM recommendations on hot *Ziabites* for new T1DM, until higher levels of evidence are provided, it should never replace insulin in hyperglycemic conditions and just can be used as a complementary management.

Although the complete profile of Mizaj in DM has not been explained in classic medicine, it has been linked to impairments in temperature regulation recently,^[2,21] so it can be related to something near to the definition of sue Mizaj. There are a considerable number of studies that investigated the relationship between pathophysiologic aspects of impaired thermoregulatory function and DM.

Studies in agreement with cold *Ziabites*

Some studies showed that vasomotor and sudomotor dysfunctions in T1DM patients lead to impaired skin blood flow and sweating during heat stress.^[22,23] This may cause decrease in skin temperature.^[24] On the other hand, impairment of heat conservation may contribute to and could be a consequence of autonomic neuropathy.^[21] Along with these reports, several studies reported decrease in core body temperature and skin temperature in diabetic patients in comparison to healthy control groups.^[22,24] These findings, however, may be related to cold *Ziabites* and are in agreement with the findings from the current study on chronic T1DM patients.

Studies in agreement with hot *Ziabites*

Studies revealed that individuals with T1DM had greater skin and limb blood flow relative to healthy controls, which is thought to be related to moderate vasodilation induced by a general hyperinsulinemic state,^[2] and therefore, diabetes tends to place individuals at greater risk for heat-related illness during heat waves and physical activity due to an

impaired capacity to dissipate heat.^[2,23] These observations can be related to hot *Ziabites* and are in agreement with the findings from the current study on new T1DM patients.

In addition, according to PM principles, dissimilar conditions of samples about Mizaj interfering factors such as duration of DM, presentation of diabetes complications, blood glucose level, and using different doses of drug (insulin) in different studies all might contribute to such conflicting results. In agreement with this idea, similar to our findings, in chronic T1DM group, Scott *et al.* showed that shivering or falling in core temperature in response to the acute cold stress was done only in diabetics with neuropathy because of impairment of reflex vasoconstriction in the limbs. Diabetics without neuropathy and nondiabetics neither shivered nor dropped core temperature.^[21]

Our study had some limitations, such as lack of specific method or tool available for Mizaj determination of *Ziabites* in children to be used in the study.^[25] Therefore, we had to use the MMQ which is only standard Mizaj identification measure which its psychometric properties are well documented.^[4] We suggest to design a specific instrument to determine the Mizaj of *Ziabites*.

CONCLUSION

The study findings indicated that children with new type 1 diabetes were hotter and dryer in Mizaj versus chronic T1DM that were colder than controls. Therefore, PM recommendations on Mizaj may improve the health condition of DM patients, and more investigations are strongly suggested. Furthermore, our data indicated that MMQ was an appropriate instrument to measure the Mizaj of diabetic patients.

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Conflicts of interest

There are no conflicts of interest.

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Appendix: Mojahedi Mizaj questionnaire

Question number	Question phrase	Hot/cold subscale ^a		
		1	2	3
Q1	When others touch your skin, what do they say about its hotness or coldness?	Cold	Tampere	Hot
Q2	How big is the palm of your hand?	Small	Not small, not big	Big
Q3	How fast are you influenced by hotness and coldness?	I feel cold, fast	I feel the same in both cases	I feel hot, fast
Q4	How fast are you influenced by hot nature foods as honey, spices, paper or cold nature foods as buttermilk, yogurt and cucumber?	I feel cold, fast by cold nature foods	I feel the same in both cases	I feel hot, fast by hot nature foods
Q5	How is your voice power compared to others?	Weak	Not weak, not strong	Strong
Q6	How do you pronounce several consequent sentences?	Articulate	Not articulate, not continuous	Continuous
Q7	How is your rage and anger?	I get angry late	I get angry no late no fast	I get angry fast
Q8	How is your physical movements compared to others?	Very slow	Not slow, not fast	Fast
Wet/dry subscale^b				
Q9	How is the condition of your skin's softness and dryness?	Very soft	Not soft, not dry	Very dry
Q10	Are you fat or thin compared to others?	Very fat	Not fat, not thin	Very thin

^aThe score of hot/cold scale could be 8–24. Hot ≥ 19 , cold ≤ 14 , ^bThe score of wet/dry scale could be 2–6. Dry ≥ 5 , wet ≤ 3