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Assessment of autonomic neuropathy in type 1 diabetics by cardiovascular reflex testing and heart rate variability: A case series

Michelli Brants Silveira, Rodrigo de Azeredo Siqueira, Adalgiza Moreno Mafra, Antônio Marcos da Silva Catharino

ABSTRACT

In this case series the authors are using data from a survey of two patients diagnosed more than five years ago with type 1 diabetes, patient 1 was symptomatic and patient 2 was asymptomatic for diabetic autonomic neuropathy. The heart rate variability (HRV) analysis involved time and frequency domains; for the time domain, with the indexes RR intervals between normal heartbeat (SDNN), pNN50, square root of the sum of the square of the difference between iRR (RMSSD). The HRV test showed that in the time domain, patient 1 presented a RMSSD slightly higher than the SDNN value, which means more vagal control over cardiac function; however, the PNN50% value did not indicate this parasympathetic activity. Patient 2, on the other hand, presented an SDNN higher than the RMSSD, indicating prevalence of sympathetic stimulation over the heart. When we look at the frequency domain, we can confirm the high influence of the parasympathetic system with a variable of high frequency (HF) higher than low frequency (LF), which represents sympathetic activity. In contrast, the asymptomatic patient showed prevalence of sympathetic activity with LF extremely higher than HF. In the analysis of the breath test and the waltz test, we observed an alteration in the result of the symptomatic patient, reaching a rate lower than expected for his age. On the other hand, the asymptomatic patient was above the expected rate. In conclusion, symptomatology is a striking feature in the diagnosis of diabetic autonomic neuropathy. Cardiovascular reflex tests are essential to close the diagnosis, and to evaluate and diagnose the asymptomatic cases that may be present.

Keywords: Cardiovascular system, Diabetes mellitus type 1, Diabetic neuropathies, Heart rate

Michelli Brants Silveira[1], Rodrigo de Azeredo Siqueira[2], Adalgiza Moreno Mafra[3], Antônio Marcos da Silva Catharino[4]

Affiliations: [1]Professor, Doctor of Medicine, Universidade Iguaçu - UNIG, Nova Iguaçu, Rio de Janeiro, Brazil; [2]Medical Student, Universidade Iguaçu - UNIG, Nova Iguaçu, Rio de Janeiro, Brazil; [3]Coordinator of the Undergraduate Physiotherapy, Universidade do Iguaçu, Nova Iguaçu, Rio de Janeiro, Brazil; [4]Hospital Geral da Nova Iguaçu - Nova Iguaçu - RJ, Brazil; School of Medicine - UNIG - RJ, Brazil.

Corresponding Author: Antônio Marcos da Silva Catharino, Rua Gavião Peixoto 70, Room 811, CEP 24.2230-100, Icaraí, Niterói-RJ, Brazil; Email: catharino.antonio@gmail.com

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INTRODUCTION

Patients with diabetes mellitus suffer from pathological involvement of the nervous system. Autonomic neuropathy is a dysfunction of the nerves that has the function of regulating functions such as perspiration, blood pressure, and heart rate. Cardiovascular autonomic neuropathy (CAN), despite being considered a common chronic complication in patients with diabetes mellitus (DM) and associated with increased cardiovascular morbidity and mortality, still remains underdiagnosed [1, 2]. The signs and symptoms associated with the presence of CAN appear late in the course of the disease, making it necessary to use cardiovascular reflex tests for early identification of CAN [3, 4]. Considering the scarcity of data in the literature on the prevalence of CAN in the Brazilian population with type 1 DM (DM1), this case series has a relevant role in the early identification of this complication as well as the determination of possible clinical and laboratory factors related to its presence.

The prevalence ranges from 2.6% to 90% among patients with DM [5], depending on the diagnostic method used and increases with age, duration of diabetes, and presence of inadequate glycemic control [6]. It is usually associated with peripheral sensory-motor neuropathy of the lower limbs (in up to 62.5% of cases) as well as with the presence of other cardiovascular risk factors (CVR), such as hypertension, dyslipidemia, diabetic nephropathy and retinopathy, and peripheral vascular disease (PVD).

Cardiovascular autonomic neuropathy has been pointed out as one of the possible causes of sudden death and represents a strong predictor of CVR in both DM1 and DM2. Diabetic patients with coronary artery disease (CAD) have mortality rates of 16–53% in five years, depending on the severity of the CAD. In the DIAD study (detection of silent myocardial ischemia in asymptomatic diabetic subjects), carried out in patients with DM2, the presence of CAN, determined by the reduced Valsalva's ratio, was predictive of silent myocardial ischemia, regardless of the presence of traditional RCV factors such as high blood pressure (HBP), age, gender, and smoking. In the EURODIAB (European Epidemiology and Prevention of Diabetes) study, CAN was identified in 1/3 of patients with DM1 and was associated with other CVR after adjustment for age, glycated hemoglobin (HbA1c) levels, and duration of diabetes [3]. Data from the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study demonstrated that patients with CAN had a mortality rate about 1.55–2.14 times higher than patients without CAN.

Considering the scarcity of data in the literature on the prevalence of CAN in the Brazilian population with DM1, this case series have a relevant role in the early demonstration of this complication.

CASE SERIES

This case series will report two clinical cases of patients diagnosed with diabetes mellitus type 1 (DM1) for over five years, where patient 1 presented alterations in the Ewing test, for evaluation of diabetic autonomic neuropathy and heart rate variability (HRV). And patient 2 was presented within the normality standard.

Patient 1 was a 25-year-old Caucasian female, who diagnosed with DM1 14 years ago, was overweight [body mass index (BMI) 27.0], abdominal circumference 108 cm, normotensive, normocardic, normoglycemic, denied hypertension, alcoholism, and smoking, and practiced physical activity regularly. She reported symptoms such as dyspnea, dizziness, visual disturbances, pre-syncope when standing, constipation, urinary incontinence, polyuria, urinary urgency, repeated urinary tract infection, and hyperhidrosis. She has no other comorbidities.

Patient 2 was a 20-year-old Caucasian male, who diagnosed with DM1 seven years ago, presented with ideal weight (BMI 21.1), abdominal circumference 84 cm, normotensive, normocardic, normoglycemic, denied hypertension, alcoholism, and smoking, and practiced physical activity regularly. As for the symptoms questionnaire, he was asymptomatic. He denied any associated comorbidities.

DISCUSSION

Both the patients were evaluated on the same day, and were previously instructed not to ingest caffeine, alcoholic beverages, and oral medications such as antidepressants, anxiolytics, and cardiovascular drugs, for a period of 8 hours before the tests and the suspension of physical activity for 24 hours.

We show in images the graphs from the Polar Flow system acquired during the tests. In Figure 1 we present the HRV analysis of patient 1 and in Figure 2 the same analysis of patient 2. We excluded the first 5 minutes and the final 5 minutes.

The HRV analysis involved time and frequency domains. For the time domain, the following indices were selected.

- SDNN: RR intervals between each normal heartbeat, expressing sympathetic nervous system interference in the heart.
- pNN50: percentage of adjacent iRR (interval between two waves r) values greater than 50 ms. Represents parasympathetic influences on iRR, because actions controlled by the parasympathetic nervous system are faster than those modulated by the sympathetic nervous system; when greater than 50 ms, they may signify greater vagal interference in heart function.
- RMSSD: square root of the sum of the square of the difference between iRR. Similar to pNN50, RMSSD expresses parasympathetic nervous system interference in the heart, and the higher its value, the greater the vagal action in the heart.

For the frequency domain we use the variables described below:

LF: low frequency component (0.04–0.15 Hz), whose values express sympathetic cardiac tonus, although some authors report a certain vagal influence on these values.

HF: high frequency component (0.15–0.4 Hz), whose values express parasympathetic cardiac tonus.

In the analysis of the data described in Table 1, it shows that patient 1 presented results regarding the

Figure 1: Variation of heart rate in patient 1, image acquired by the Polar Flow system.

Figure 2: Variation of heart rate in patient 2, image acquired by the Polar Flow system.

time analysis within the parameters of normality, which indicates that the cardiac automatism is under influence of the sympathetic nervous system that is superposing the parasympathetic system. Patient 2, on the other hand, presents with altered results, i.e., higher than the normality level, mainly in pNN50 with a value of 0.56 heart. Remembering that values higher than 0.50 represent the parasympathetic influences in the iRR, because the actions controlled by the parasympathetic nervous system are faster than those modulated by the sympathetic nervous system; when greater than 50 ms, they can mean greater vagal interference in the functioning of the heart.

Cardiac activity during the orthostatism test, for patient 1 is shown in Figure 3 and the same result for patient 2 is shown in Figure 4. This test is altered for the two patients analyzed, showing a bradycardia in the first minute that represents a higher than expected vagal activity, which is demonstrated in Table 2, should be between 1.17 for both the patients. Patient 1 presented the index of 1.34 already whereas patient 2 with the value of 1.42, as already reported higher than normal indices.

The third test to which they were submitted was the respiratory test, where Figure 5 demonstrates the outcome of patient 1 and Figure 6 of patient 2. Table 3 shows the analysis of the graphics and calculation of the respiratory coefficient. It is noted that only patient 2 achieves the expected coefficient for age.

Figures 7 and 8 show the Valsalva test result of patients 1 and 2, respectively. Table 4 shows the result obtained and the expected for normality according to age.

We used results from two patients where one was symptomatic and the other was asymptomatic for autonomic neuropathy. They were approximately the same age, which may have interfered in the symptomatology that is the duration of the DM1.

The HRV test showed that in the time domain, patient 1 presented a RMSSD slightly higher than the SDNN value, which means more vagal control over cardiac function; however, the PNN50% value did not indicate this parasympathetic activity. Patient 2, on the other hand, presented an SDNN higher than the RMSSD,

Table 1: Cardiac frequency variability showing the HRV results, comparing the results of the two patients, in time domain frequency

Patient 1				**Patient 2**			
Time domain				**Time domain**			
Variable	Units	Values		Variable	Units	Values	
SDNN	ms	10.5		SDNN	ms	28.4	
RMSSD	ms	10.7		RMSSD	ms	19.8	
PNN50%	%	0.00		PNN50%	%	0.56	
Frequency domain				**Frequency domain**			
Variable	Units	LF	HF	Variable	Units	LF	HF
Freq.	Hz	0.04–0.15	0.15–0.40	Freq.	Hz	0.04–0.15	0.15–0.40
Freq. peak	Hz	0.123	0.243	Freq. peak	Hz	0.040	0.150
Power	m/s	37	40	Power	m/s	882	93

Abbreviations: ms, milliseconds; Freq., frequency; SDNN, RR intervals between normal heartbeat; RMSSD, square root of the sum of the square of the difference between iRR; PNN50%, percentage of adjacent iRR values greater than 50 ms; LF, low frequency; HF, high frequency; HRV, heart rate variability.

Table 2: Results of the orthostasis test of the two patients evaluated

ID	Orthostatism	Normality	Age
Patient 1	1.34	1.17	25
Patient 2	1.42	1.17	20

Table 3: Respiratory test results of the two patients evaluated

ID	Breath test	Normality	Age
Patient 1	1.19	1.2	25
Patient 2	1.88	1.23	20

Table 4: Result of the Valsalva test performed by the two patients

ID	Valsalva test	Normality	Age
Patient 1	1.35	1.5	25
Patient 2	1.89	1.5	20

Figure 3: Patient 1's orthostasis test.

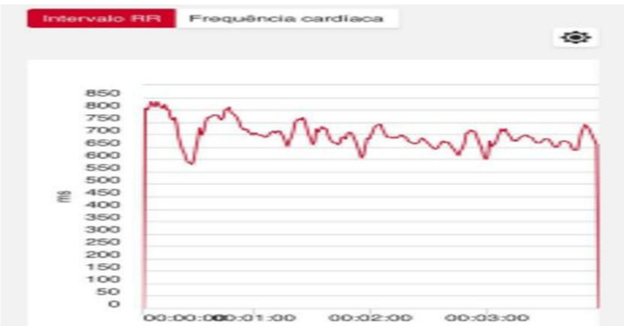

Figure 4: Patient 2's orthostasis test.

Figure 5: Patient 1's breath test.

Figure 6: Patient 2's breathe test.

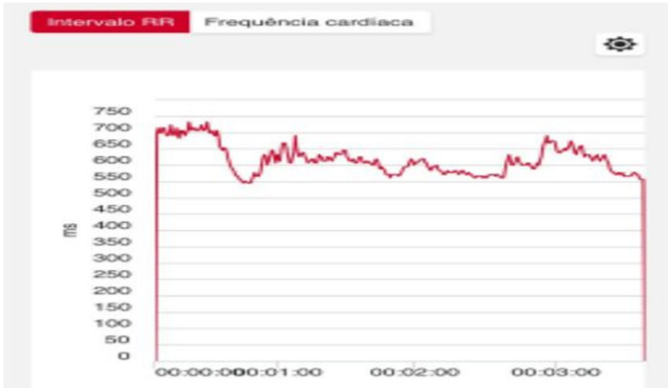

Figure 7: Patient 1's sallow test, shown through the Polar Flow system image, shows that there is a drop in heart rate during the sallow maneuver.

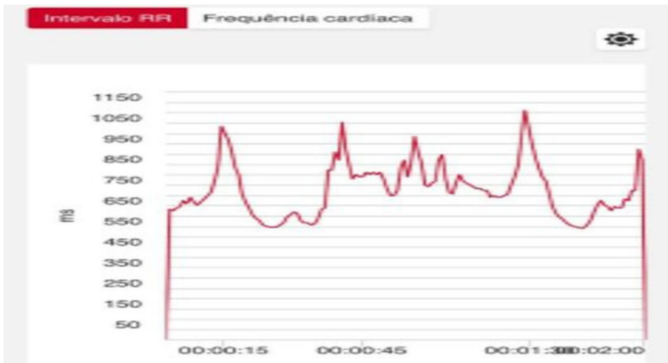

Figure 8: Patient 2's Valsalva test, acquired by the Polar Flow system, shows a reduction in heart rate during both moments of the Valsalva maneuver.

indicating prevalence of sympathetic stimulation over the heart. When we look at the frequency domain, we can confirm the high influence of the parasympathetic system with a variable of HF higher than LF, which represents sympathetic activity. In contrast the asymptomatic patient showed prevalence of sympathetic activity with LF extremely higher than HF [1, 2].

In the orthostatic and postural hypotension tests, the patients showed indices within the normal range [7].

In the breath test and the waltz test, we observed an alteration in the results of the symptomatic patient, reaching an index lower than expected for his age. On the other hand, the asymptomatic patient was above the expected index. These tests evaluate the parasympathetic component of the autonomic nervous system. The result of two altered tests confirms the diagnosis of CAN [4, 5].

CONCLUSION

Symptomatology is a striking feature in the diagnosis of diabetic autonomic neuropathy. Ewing's tests are essential to close the diagnosis, and also to evaluate and diagnose the asymptomatic cases that may be present.

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Author Contributions

Michelli Brants Silveira – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Rodrigo de Azeredo Siqueira – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Adalgiza Moreno Mafra – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

ABOUT THE AUTHORS

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Michelli Brants Silveira, Medical Student at Universidade Iguaçu - UNIG, Nova Iguaçu, Rio de Janeiro, Brazil. She is a physiotherapist at the Estate de Sá University, Niteroi/RJ, Brazil. She holds a post-graduate degree in intensive therapy. Currently, she is pursuing her fifth year course in medicine at the University of Iguaça, Nova Iguaçu, Brazil. Being in this same institution, she has received a scholarship by the university in the research program for two years.
Email: michellibrants@hotmail.com

Rodrigo de Azeredo Siqueira, Professor, Doctor of Medicine, Universidade Iguaçu - UNIG, Nova Iguaçu, Rio de Janeiro, Brazil. He holds a PhD in Endocrinology from UFRJ (Federal University of Rio de Janeiro), Rio de Janeiro, Brazil. He has published 12 research papers in national and international academic journals and is the author of 3 books. His research interests include diabetes, obesity, and dyslipidemia. It intends to guide research in the diabetes landscape in the future.
Email: rodrigoendocrinologista@gmail.com

Adalgiza Moreno Mafra, Coordinator of the Undergraduate Physiotherapy at Universidade do Iguaçu, Nova Iguaçu, Rio de Janeiro, Brazil. She holds a PhD in Cardiological Sciences from Universidade Federal Fluminense - 2013. She has published 68 research papers in national and international academic journals and is the author of 3 books. She is a research coordinator at Universidade Iguaçu and develops research in metabolic, neurological, and cardiorespiratory diseases.
Email: adalgizamoreno1@gmail.com

Antônio Marcos da Silva Catharino, PhD student in Neurology at the Federal University of the State of Rio de Janeiro - UNIRIO, Adjunct Professor of Medicine at Iguaçu University - UNIG/Nova Iguaçu, RJ, Brazil. He is the member of the Brazilian Academy of Neurology. He is the founding Member of the Neurology Association of Rio de Janeiro state. He graduated in Medicine from the Iguaçu University (1997), Master in Neurology from the Federal University of the State of Rio de Janeiro - UNIRIO (2006), and Master in Education from the Iguaçu University (2002). Currently, he is a professor of the disciplines of Medical Semiology and Clinical Medicine/Neurology at Iguaçu University, where he also guides Scientific Initiation works. It maintains a channel of classes of Neurology on YouTube (Dr Antonio Catharino - Neurologist). He has experience in the field of Medicine-Neurology, with emphasis on headaches. He is a physician at the Neurology Service of the General Hospital of Nova Iguaçu, Organizer of the Headache Outpatient Clinic at Gaffre-Guinle Hospital in 2006. He was approved in second place in the competition public of the Mesquita City Hall for the role of Medical-Neurologist, in 2006; approved in the first phase of the public contest for Physician-Neurologist of the Sarah Network, in 2006; approved in first place in the contest of the Niterói City Hall for the role of Medical-Neurologist, in 2007; approved in second place in the public contest of the City Hall of Duque de Caxias for the function of Physician-Neurologist, in 2007; approved in fifth place in the public contest of the City Hall of Rio de Janeiro for the function of Doctor-Neurologist, in 2008; approved in third place in the public contest of the State Department of Health and Civil Defense of Rio de Janeiro for the position of Medical-Neurologist, in 2009.
Email: catharino.antonio@gmail.com

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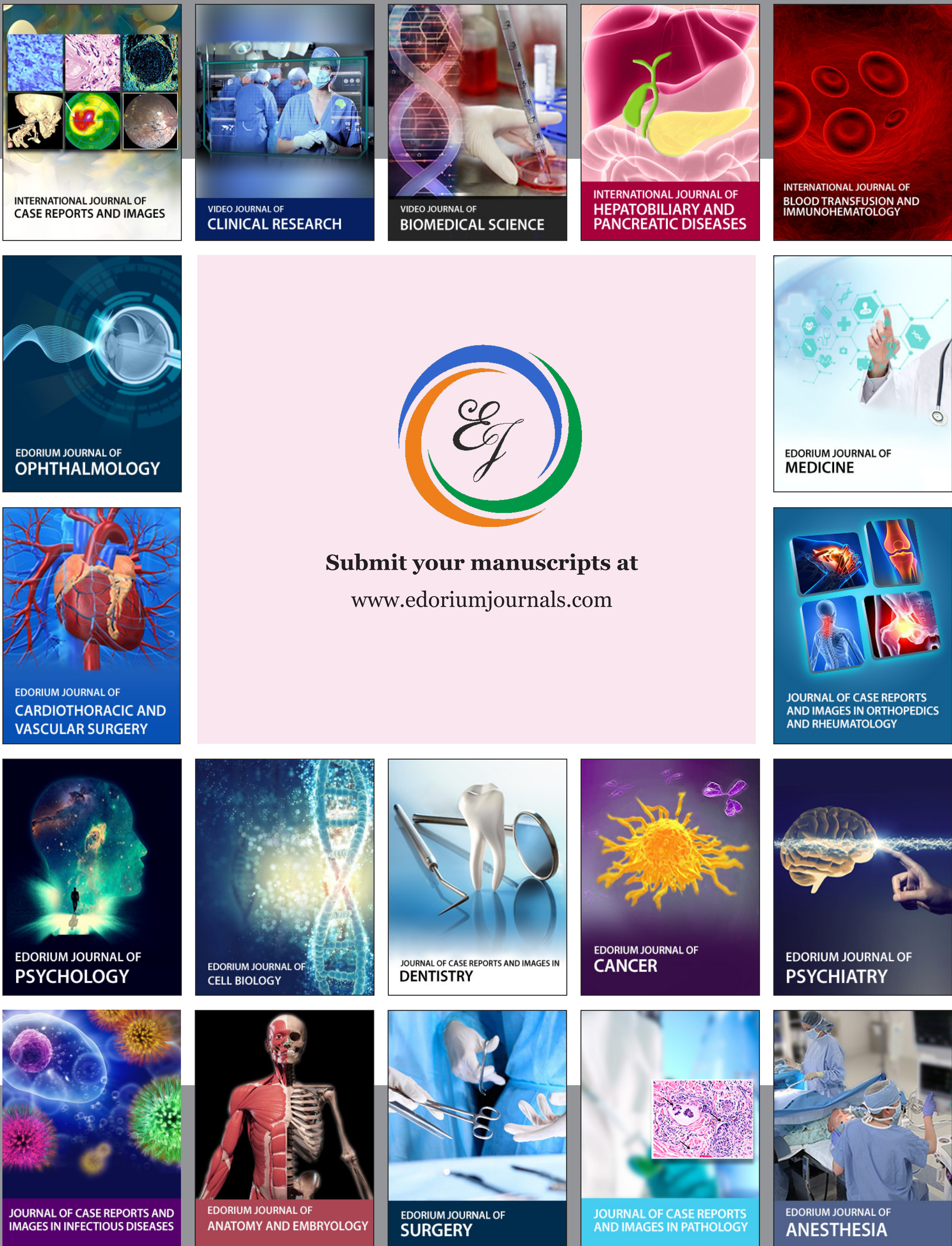
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