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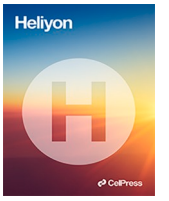

Research article

Assessment of adherence to carbamazepine using plasma and saliva samples, a study from Jordan

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ABSTRACT

Background: The measurement of carbamazepine levels in a biological sample is required to guide dosing, and prevent toxicity, and can be useful to assess medication adherence.
Aim: The primary aim of the presented study is to analyze carbamazepine levels in saliva and plasma samples of outpatients and to assess adherence to carbamazepine using saliva and plasma levels.
Methods: Adults who used carbamazepine for at least one month were recruited from the outpatient clinic department of Princess Basma Hospital, a public hospital in Irbid. Saliva and blood samples (1 ml) were collected simultaneously from subjects, and using a microanalytical method with high-performance liquid chromatography coupled with an ultraviolet detector, the level of carbamazepine (in micrograms per milliliter) was ascertained. Analysis of adherence to carbamazepine was carried out using plasma and saliva levels.
Results: A total of 69 consecutive patients attending the neurology clinic were recruited, of whom 85.5% had epilepsy. Approximately one-third (34.8%) used carbamazepine as monotherapy, whereas the remainder used a combination of antiepileptic drugs to control seizures. Overall, about two-thirds (71.9%) of the studied samples were non-adherent in either plasma or saliva samples. By referring to the plasma sample carbamazepine concentration, 75.4% of the respondents were adherents, 15.9% had under-adherence, and 8.7% had over-adherence. A total of 85.9% of the responders were adherent using the carbamazepine level in saliva samples. Plasma and saliva carbamazepine levels were linearly correlated to one another. Polypharmacy was commonly utilized with the patients, as 42% of the patients used two medications, with a range of 1–7 drugs used concomitantly. The predictor associated with higher plasma and saliva carbamazepine levels, as determined by multiple linear regression analysis, was the occurrence of seizures less than once a month, as compared to seizures with higher frequencies.
Conclusion: Saliva carbamazepine levels show the potential to be used as an alternative matrix to assess medication adherence, with a considerable correlation with the plasma carbamazepine level. Healthcare professionals can address routine care non-adherence through such measures.

1. Introduction

Carbamazepine is an effective antiepileptic medication for a variety of seizure disorders. Other uses of carbamazepine includes

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treatment of trigeminal neuralgia and bipolar disorder. The antiepileptic spectrum of carbamazepine includes partial and generalized seizures [1]. Carbamazepine and other antiepileptic drugs might require the use of therapeutic drug monitoring, to ensure drug effectiveness without causing toxicity [2,3]. Measuring plasma carbamazepine levels is crucial, particularly when there is a possibility of drug interaction or toxicity [3]. Measuring drugs in saliva can serve as an alternative modality for measuring drug concentration in body fluid, which is useful for therapeutic drug monitoring. Such an approach can allow for non-invasive home sampling, which the patient might prefer over traditional blood sampling, especially children [4,5].

Medication adherence is one of the important prerequisites for drug efficacy. Non-adherence to prescribed drug therapy may lead to unfavorable outcomes, including decreased medication effectiveness and increased risk of disease progression and complications [6, 7].

Traditionally, carbamazepine requires therapeutic drug monitoring (TDM) for dosing optimization, in order to maximize disease control and decrease toxicity using venous blood samples [2]. However, saliva can be used to measure drug concentrations, and can be possible to be used in therapeutic drug monitoring for certain medications. If there was strong correlation between the drug's concentration in the saliva and its plasma concentration, this sampling technique would be extremely beneficial [5–8].

Saliva samples offer numerous potential advantages for measuring drug concentrations: they are non-invasive, cause minimal burden and discomfort, and can be collected at home [9,10]. A significant benefit of a saliva sample is that it evaluates the concentration of the drug's physiologically active and free concentration [10]. It has been well known that the free concentration of a drug in biological fluids is important in determining the clinically relevant behavior of drugs, such as their interaction with receptors [11,12]. The identification of free drug concentration is important when it comes to therapeutic drug monitoring (TDM), which determines the activity and toxicity of drugs. This is critical for a drug that requires TDM, such as anti-epileptic drugs (AEDs) [13]. Furthermore, saliva samples can identify non-adherence to medications, a detrimental patient misbehavior that impairs disease control and increases the chances for disease complications and progression [6,14]. In routine care, healthcare professionals simply ask the patient directly about adherence to medicines, and since this question relates to a sensitive and possibly shameful issue, most patients will deny non-adherence.

As a means to improve the correct identification of non-adherence, objective measures of adherence, and provide an accurate assessment of adherence in patients, health professionals must drug concentrations from body fluid samples [15]. Traditionally, direct measurement of adherence of patients utilizes venous blood samples. However, this technique is invasive that typically necessitates involvement of healthcare professionals to collect the sample. To combat this, saliva sampling proves useful for the assessment of adherence. The direct patient care application of such an approach can help identify and flag potential medication-related problems, such as toxicity and underdosing, through the use of home sampling. Previous studies assessed the concentration of carbamazepine in plasma samples, but most were aimed at developing analytical methods for measuring carbamazepine in plasma and saliva samples [16–21]. A number of studies were conducted comparing plasma and saliva concentrations, and showed an acceptable correlation for carbamazepine, in which many studies focused on pediatric patients [4,22,23]. However, f ew studies were carried out to specifically measure the carbamazepine level in plasma and saliva samples, and none of these studies were carried out in Jordan [24]. The primary aim of the present study is to measure carbamazepine levels in saliva and plasma samples of patients through the employment of an analytical method, and to, correlate the results obtained from saliva to those measured in plasma, and finally, to assess the adherence to carbamazepine within the study participants using direct objective saliva and plasma samples.

2. Methods

The present study was across-sectional study was carried out in the period January–June 2022, in the outpatient clinic's department at Princess Basma Hospital, a 500-bed public hospital in Irbid, a large city north of Jordan. The present study was approved by the Institutional Review Board of the Jordan University of Science and Technology (ref.: 4/115/2018) and the Ministry of Health (Ref.: MOH REC 1800129) which oversees the hospital. The study involved in the assessment of the blood and saliva concentrations of carbamazepine using the appropriate instrumental analysis method, and adherence to carbamazepine was assessed using direct plasma and saliva levels.

In the Pharmaceutical Research Center Laboratory in Jordan University of Science and Technology, carbamazepine levels in plasma and saliva were analyzed using a high-performance liquid chromatography technique.

2.1. Data collection

Participating medical practitioners in the neurology department were asked to join the study in order to facilitate the recruitment of research subjects. A trained research assistant, with a MSC degree in Clinical Pharmacy and research experience, screened the potential participants attending the neurology outpatient clinic for eligibility for the study. The criteria for selection of participants were.

- The inclusion criteria: Patients more than 18 years old who were prescribed carbamazepine and have used it for at least one month.
- The exclusion criteria: Those who could not provide informed consent (for example Alzheimer's disease), were excluded from the study.

While patients were waiting for their appointment, potential participants were approached by the research assistant. The study was explained and the patient information leaflet was issued to them. The participants were informed about the voluntary nature of participation, which they can withdraw at any time and the confidentiality of the response will be ensured. After consideration,

patients were asked to take part in the study, and only those who agreed to take part were asked to provide written informed consent. A copy of the informed consent was filed in patient medical notes. After recruitment of the patients, All data were collected using standardized data collection forms; via referral to medical notes (paper-based or electronic), asking participants, and getting information from the healthcare team.

Sample size estimation: The sample included epileptic patients who used carbamazepine from one neurology clinic, few patients were taking carbamazepine and the number of patients taking carbamazepine is unknown. All patients fulfilling the selection criteria were asked to participate, thus in the present study the total number of patients included was limited to 69 patients. During the last month of the recruitment, there was no additional patient meeting the inclusion criteria, and the recruitment was halted with the present sample size achieved.

Saliva and blood samples (1 ml) were collected simultaneously from subjects, writing the patient study number and the collection time on the label. Collected samples (saliva and blood) were stored at −80 °C for the analysis phase of the project. Preparation for the blood sample prior to freezing involved centrifugation of blood components, leaving only the plasma component. A standard instrumental analysis technique was carried out to measure the saliva and plasma carbamazepine levels [24,25]. After ending the recruitment period, all the stored samples (plasma and saliva) were analyzed using a microanalytical method with high-performance liquid chromatography coupled with an ultraviolet detector (HPLC-UV), and the level of carbamazepine (in microgram per milliliter) was determined. Correlation analysis between saliva and blood carbamazepine levels were carried out as well.

2.2. High-performance liquid chromatography technique

In the analytical phase of the project, a microanalytical method using high-performance liquid chromatography was utilized keeping in line with a published method in the research literature [26]. Carbamazepine standard was used together with acetonitrile HPLC grade was purchased from MERCK, ultrapure water was locally prepared in the lab, autosampler vials 1.5 ml and flat bottom glass insert 250 μl. The instrument used for the present study was UHPLC Thermo-Dionex Ultimate 3000 made in Germany. Separation was achieved using C18 column HiQ sil KYA Japan 4.6 mm × 250 mm 5 μm, the mobile phase consisted of acetonitrile and water in the ratio 35:65 passed through a 0.45 μm membrane and delivered at flow rate 1.6 ml/min and the UV detector was set at 285 nm. As described by Johnston and Lester [26], 100 μl plasma was pipetted and placed in an Eppendorf tube 1.5 ml and 100 μl acetonitrile were added to precipitate proteins by vigorous shaking using a vortex mixer for a few seconds finally the tube was centrifuged at 12000 rpm and the supernatant was placed in flat bottom glass insert 250 μl and 100 μl was injected in UHPLC system.

2.3. Study measures

Analysis of adherence to carbamazepine was carried out using direct methods that measured plasma and saliva carbamazepine levels in recruited patients.

The patient was considered non-adherent if at least one of the objective assessment methods (plasma or saliva concentrations) showed that the patient is non-adherent. The cut-off-point for non-adherence was.

- Blood sample level out of the range of 3.2–13.2 mg/L (corresponding to 80%–120% of the therapeutic level of 4–12 mg/L)
- Saliva sample level out of the range of 0.4–4.8 mg/L (corresponding to 80%–120% of the therapeutic level of 0.5–4.0 mg/L)

2.4. Data analysis

Data were analyzed using SPSS version 22. Descriptive statistics, i.e., means and frequencies were used to summarize the data. Differences between variables were assessed using independent samples *t*-test, chi-square test, and the Fisher exact test. The plasma and salivary carbamazepine levels were selected as a proxy for medication adherence, and linear regression analysis was utilized to identify predictors associated with higher plasma and salivary concentrations. Various background, demographic and clinical data that were plausible to be associated with higher plasma and salivary carbamazepine were considered and tested for possible association using an automatic linear regression analysis. leaving statistically variable associated with higher plasma and salivary levels. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Demographics and disease characteristics

A total of 69 consecutive patients attending the neurology clinic were recruited. The study sample was almost equally distributed between males and females (males = 43.5%). A total of 30.4% of the study sample were less than 30 years old, and approximately one quarter were in their thirties, another quarter were in their forties, one-tenth in their fifties, and a few (2.9%) were more than 60 years old. About sixty (58.0%) percent of the samples were married. The diagnosis for carbamazepine use was epilepsy in 85.5% of the samples and few patients had other diagnoses for carbamazepine use, such as electrical shock (n = 1), neuropathic pain (1), neuropathy (1), seizures due to accidents (2), seventh nerve palsy (1) and trigeminal neuralgia (4). A total of 26.9% of the sample had a disease duration of less than 5 years, 22.4% from 5 to 9 years, 10.4% from 10 to 14 days, 11.9% from 15 to 19 years, 7.5% from 20 to 24 years, and 20.9% more than 25 years. The majority of the patients were using 1200 mg of carbamazepine per day. The patients in the

Table 1
Demographics and disease characteristics.

Variable	Frequency (n (%))
Gender	
Male	30 (43.5)
Female	39 (56.5)
Age (years)	
less than 30	21 (30.4)
30–39	18 (26.1)
40–49	18 (26.1)
50–59	10 (14.5)
60 and more	2 (2.9)
Marital status	
Single	29 (42.0)
Married	40 (58.0)
Diagnosis	
Epilepsy	59 (85.5)
Electrical shock	1 (1.4)
Neuropathic pain	1 (1.4)
Neuropathy	1 (1.4)
Seizures due to accident(s)	2 (2.9)
Seventh nerve palsy	1 (1.4)
Trigeminal neuralgia	4 (5.8)
Disease duration (years)	
Less than 5	18 (26.9)
5–9	15 (22.4)
10–14	7 (10.4)
15–19	8 (11.9)
20–24	5 (7.5)
25 or more	14 (20.9)
Current total carbamazepine dose (mg)	
400.00	17 (25.0)
600.00	4 (5.9)
800.00	14 (20.6)
1200.00	29 (42.6)
1600.00	3 (4.4)
2400.00	1 (1.5)
Number of Antiepileptic drugs	
1	24 (34.8)
2	30 (43.5)
3	13 (18.8)
4	2 (2.9)
Other antiepileptic drugs used	
Valproic acid	20 (29.0)
Lamotrigine	9 (13.0)
Levetiracetam	22 (31.9)
Clonazepam	5 (7.2)
Phenytoin	2 (2.9)
Gabapentin	3 (4.3)
Frequency of seizures	
Seizure free	14 (21.5)
Daily	2 (3.1)
2-3 times weekly	7 (10.8)
Weekly	3 (4.6)
Monthly	13 (20.0)
Less than monthly	26 (40.0)
Total Number of drugs	
1	20 (29.0)
2	29 (42.0)
3	10 (14.5)
4	6 (8.7)
5	2 (2.9)
6	1 (1.4)
7	1 (1.4)
Other disease present	
No other disease	60 (87.0)
Brain tumor	1 (1.4)
Diabetes Mellitus	2 (2.9)
Hypertension	5 (7.2)
Osteoporosis	1 (1.4)
Asthma	2 (2.9)

(*continued on next page*)

Table 1 (*continued*)

Variable	Frequency (n (%))
Hypothyroidism	1 (1.4)
Pregnancy	4 (5.8)
Peptic ulcer disease	2 (2.9)

present study were using other antiepileptic drugs to stabilize the patient; 34.8% of the patients were using one antiepileptic drug (carbamazepine), whereas (43.5%) reported using two antiepileptic drugs. Other common antiepileptic drugs used were levetiracetam (31.9%), valproic acid (29.0%), and lamotrigine (13.0%). A considerable number (21.5%) of patients were seizures-free. Less than half of the patients (40%), have seizures less than monthly. As a mean for ascertaining the comorbidity level in patients, the total number of drugs was recorded, with most of the patients using two medications (42.0%) and the number of medications used ranged from 1 to 7 drugs. The majority of the respondents had no other diseases. Other common diseases present were hypertension (n = 5) and diabetes mellitus (2). Four (5.8%) patients were pregnant. Full details regarding demographics and disease characteristics are provided in Table 1.

3.2. Adherence assessment

Table 2 summarizes the adherence outcomes using the plasma and saliva carbamazepine levels. Overall, about two-thirds (71.9%) of the study sample were non-adherent to any of the adherence assessment methods. By referring to the plasma sample carbamazepine concentration, 75.4% of the respondents were adherent, 15.9% had under-adherence, and 8.7% had over-adherence. A total of 10.1% of the study sample had zero levels of medication in plasma samples. Moving on to the adherence assessment using saliva samples, 85.9% of the respondents were adherent using the carbamazepine level. Eight patients had a zero level of carbamazepine in the saliva sample.

3.3. High performance liquid chromatography analysis

Fig. 1(A and B and C) illustrates the calibration curve for carbamazepine standard spiked in plasma and the typical chromatogram for the standard and plasma samples. Fig. 2 summarizes the relationship between plasma and salivary carbamazepine levels measured using HPLC (A), a plot of plasma level of carbamazepine and the administered dose (B), and the difference between plasma and saliva levels versus mean saliva and plasma levels (C). The correlation analysis between plasma and saliva carbamazepine levels (Fig. 2A) has revealed a linear relationship with an R square of 0.61 indicating the usefulness of the concept of using saliva samples for drug monitoring, which might be more convenient due to the self-sampling capability of patients. Fig. 2B further illustrates the impact of the dose on the plasma level; the data then revealed a proportional linear relationship. Fig. 2C revealed that the overwhelming majority of differences between plasma and saliva levels are located within 95% confidence interval limits.

3.4. Predictors associated with higher plasma and saliva carbamazepine levels

Table 3 summarizes the predictors associated with higher plasma and saliva carbamazepine levels. For both approaches the predictor that was statistically significant was the frequency of seizure. In particular, a statistically significant difference was present with seizures frequency that occurs less than monthly with the reference category (seizure-free), as opposed to monthly, weekly, 2–3 seizures weekly, and daily. Patients with higher plasma levels can be considered a proxy for the transition from non-adherent to adherent carbamazepine levels. As shown in the results, a seizure frequency of less than monthly was a predictor of a higher carbamazepine level in both plasma and saliva, which can indicate that a higher carbamazepine level is associated with better efficacy, decreased seizure frequency, and a more therapeutic level of the drug.

Table 2
Carbamazepine adherence results using plasma and saliva samples.

Variable	Frequency (n (%))
Adherence assessment using plasma sample	
under adherence (<80% of therapeutic level)	11 (15.9)
over adherence (>120% of therapeutic level)	6 (8.7)
adherent	52 (75.4)
plasma level equals zero	7 (10.1)
Adherence assessment using saliva sample	
under adherence (<80% of therapeutic level)	9 (14.1)
adherent	55 (85.9)
saliva level equals zero	8 (12.5)
Overall	
Overall non-adherence (shown by either assessments).	46 (71.9)

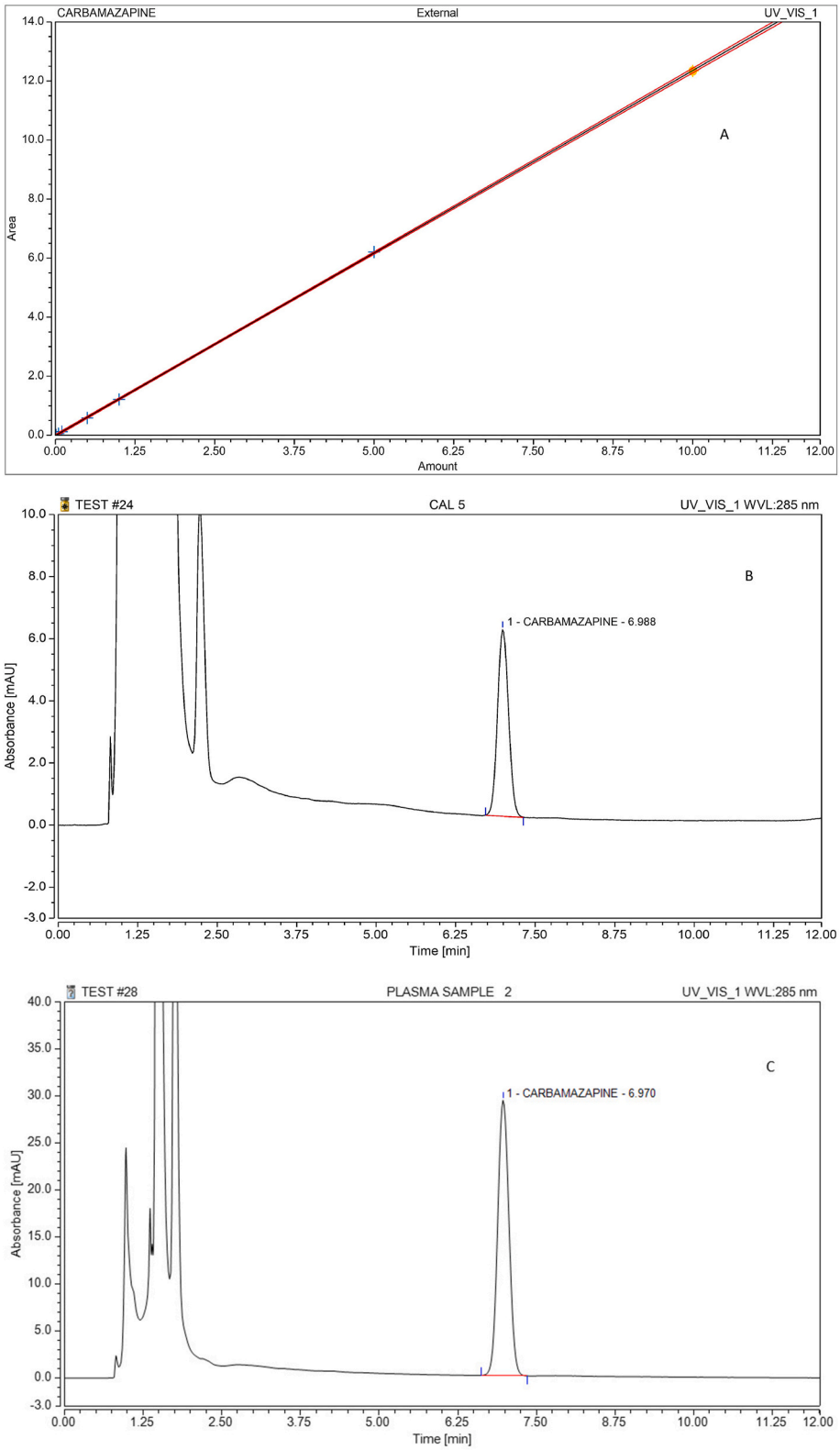

Fig. 1A. Calibration curve for carbamazepine standard spiked in the plasma,
Fig. 1B. Typical chromatogram for standard
Fig. 1C. Typical chromatogram for plasma sample.

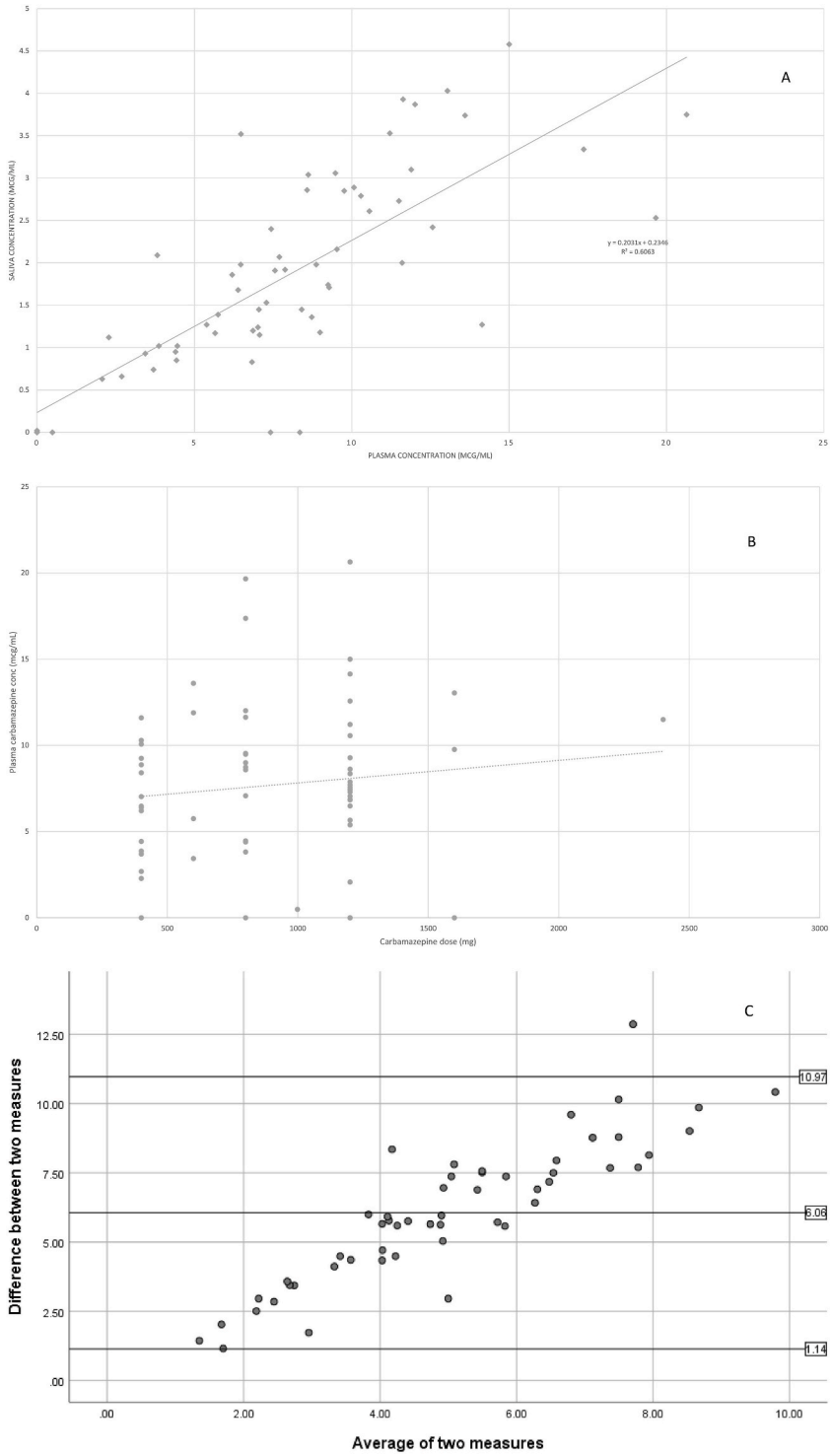

Fig. 2A. Correlation between plasma and saliva carbamazepine level measured using HPLC
Fig. 2B. Plot of plasma level of carbamazepine and administered dose.
Fig. 2C. Difference between plasma and saliva levels versus mean saliva and plasma levels.

Table 3
Predictors associated with higher plasma and saliva carbamazepine level.

Variable	B (standard error)	p value	95% confidence interval for B
Predictors associated with increased plasma carbamazepine levels			
Constant	4.704 (1.217)	<0.001	2.272–7.135
Frequency of seizures, aggregated categorical variable	0.610 (0.263)	0.023	0.085–1.135
Predictors associated with increased plasma carbamazepine levels, fine variables details			
Constant (reference, seizure free)	5.309 (1.150)	<0.001	3.008–7.610
Seizure daily	2.702 (3.253)	0.409	−3.807–9.212
2- 3 seizures weekly	0.859 (1.992)	0.668	−3.127–4.845
Seizures weekly	0.022 (2.738)	0.994	−5.456–5.500
Seizures monthly	2.617 (1.657)	0.120	−0.699–5.934
Seizures less than monthly	3.121 (1.427)	0.033	0.267–5.976
Predictors associated with increased saliva carbamazepine levels			
Constant	0.969 (0.371)	0.012	0.225–1.712
Frequency of seizures, aggregated categorical variable	0.184 (0.079)	0.023	0.027–0.341
Predictors associated with increased saliva carbamazepine levels, fine variables details			
Constant (reference, seizure free)	1.071 (0.349)	0.003	0.371–1.772
Seizure daily	0.370 (0.891)	0.680	−1.416–2.156
2- 3 seizures weekly	1.032 (0.560)	0.071	−0.092–2.155
Seizures weekly	−0.483 (0.891)	0.590	−2.269–1.303
Seizures monthly	0.498 (0.475)	0.299	−0.454–1.450
Seizures less than monthly	1.120 (0.419)	0.010	0.279–1.960

4. Discussion

This study illustrates the use of direct approaches to evaluate adherence to carbamazepine among 69 Jordanian patients (average age = 37.2 years), using the plasma/saliva level. In this study, more than half of the patients were non-adherent to any of the approaches. The highest rate of adherence was determined using saliva sampling (85.9%), followed by plasma sampling (75.4%). This highlights the potential of saliva as more convenient, due to self-sampling capability of patients and potentially being a more reliable approach for monitoring carbamazepine therapy. The correlation analysis between plasma and saliva carbamazepine levels has revealed a linear relationship with an R square of 0.61, indicating the usefulness of saliva samples for carbamazepine monitoring, which may be more convenient due to the self-sampling capability of patients.

Furthermore, the seizure frequency of less than monthly was shown to be a predictor for a higher carbamazepine level (plasma and saliva), which can indicate that a higher carbamazepine level is associated with better efficacy, decreased seizure frequency, and a more therapeutic level of the drug. This finding emphasizes the importance of individualizing therapy based on seizure frequency and medication adherence. One novel method to determine personalized therapeutic ranges and monitoring adherence to therapy is high-performance liquid chromatography coupled with ultraviolet or photodiode detection (HPLC-UV, HPLC-PDA) [27], immunoassay (FPIA) [7], gas chromatography (GC) with mass spectrometry [28] and liquid chromatography (LC) with mass spectrometry (MS) methods [29]. In the present, HPLC was used to determine the level of carbamazepine concentration in saliva. De-Diego et al. has recently developed a fast LC-UV analytical approach to determine carbamazepine level in saliva, using the RP-C18 column [30]. In agreement with our findings, a strong association was identified between serum and saliva carbamazepine concentrations.

Regarding the non-adherent behavior assessed with plasma and saliva levels, it was primarily an objective assessment method of non-adherence. There are various factors that might impact reduced adherence to medications, such as patient-related (for example, low health literacy and the use of multiple concurrent medications) [31], those related to clinicians (for example, complex drug regimen prescriptions and communication barriers) [32], and healthcare systems-related (e.g., low access to healthcare and a issues related to information technology) [33]. Thus, the key to improving carbamazepine therapy for epilepsy patients in Jordan lies in addressing these multifaceted challenges concurrently with the positive potential of saliva-based monitoring.

In this study, the vast majority of patients (85.5%) on carbamazepine were epilepsy patients, who reported taking 1200 mg of carbamazepine mg/day in divided doses. It is important to consider the implications of poor adherence for the pharmacokinetics of carbamazepine. The elimination half-life following a single oral dose of carbamazepine is approximately 35 h (range: 18–65 h). During multiple dosages, the drug's half-life is reduced to 10–20 h, most likely as a result of the autoinduction of its oxidative metabolism [34]. The risk for a subtherapeutic range of carbamazepine increased dose-dependently in daily divided dose regimens, when delayed or skipped [35]. A mailed survey has revealed that 11% increased risk of seizures after missing a dose [36]. Recurring instances of seizures can also establish a sense of fear in patients, along with increased rates of depression [37]. A previous study by Davis et al. showed that poor adherence to antiepileptic drugs was correlated with increased risk of hospitalizations (11%), higher risk emergency room (ER) visits (48%), and an annual probability of injuries from motor vehicle accidents (MVAs) rising by 44% [38]. Previous studies in Jordan were limited to qualitative assessments of patients with epilepsy. For example, the Bahou et al. study revealed high levels of depression among patients with epilepsy [39]. Although saliva-based monitoring presents a promising approach to patient-centered care, more comprehensive interventions are required to address the intricate non-adherence habits of patients. Important elements include improved patient education, enhanced clinician communication tactics customized for this particular population and individual patients, and improvements to the healthcare system that improve support and accessibility. The study revealed that a significant correlation was found between parental knowledge of epilepsy, and the level of parental education. In addition, parental

support and positive attitudes improved the overall clinical outcomes of the patients, including the control of epilepsy [40]. In agreement with previous reports, the assessment of blood drug measurements alone can be insufficient for detecting erroneous medication consumption [41], and additional approaches may need to be used to improve the clinical outcomes [42]. The most common adverse effects reported in patients on carbamazepine include memory problems, headaches, restlessness, tiredness, and depression [43,44]. Nearly 30 antiepileptic medicines (AEDs) are currently on the market, with more than two-thirds coming after carbamazepine and one-third coming after its derivative, oxcarbazepine (OXC). Although research indicates that overall AED efficacy is comparable, some newer AEDs may be more tolerable than carbamazepine [45]. The results of this study show that treatment patterns need to be changed, to make sure that approved therapy options are used most effectively in clinical practice, especially in groups that are more likely to not take their medications as prescribed.

This study paints a compelling picture of the intricate interplay between saliva-based monitoring, non-adherence, and optimal carbamazepine therapy for Jordanian epilepsy patients, in contrast to the single approach employed in previously published studies [4, 30]. The results of this study serve as guidance for healthcare facilities seeking to use saliva levels for the assessment of medication adherence. It is important to consider the limitations while interpreting the findings of this study. First, the small size of the study population. Second, only carbamazepine adherence was being evaluated; in the future, this may be expanded to include adherence to other drugs.

5. Conclusion

Direct adherence assessment of plasma and saliva levels revealed carbamazepine non-adherence in this study. Saliva or plasma non-adherence levels were high, compromising treatment outcomes. Saliva may be better than plasma levels for measuring medication adherence, according to correlation analysis. In cases of poor seizure control, healthcare professionals should consider non-adherence behavior because high plasma levels promote better adherence and lower seizure frequencies to less than monthly. These results confirm the utility of direct methods to identify carbamazepine adherence issues and help healthcare professionals address them.

Data availability statement

The authors would be happy to provide raw data upon reasonable request, in concordance with recommendations of research ethics committees and Yarmouk University.

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CRediT authorship contribution statement

Ghaith M. Al-Taani: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Alaa Yehya:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Conceptualization. **Dima Albals:** Writing – review & editing, Writing – original draft, Visualization, Resources, Project administration, Methodology, Conceptualization. **Mervat Alsous:** Visualization, Validation, Supervision, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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