Research: Treatment

Longitudinal association between medication adherence and glycaemic control in Type 2 diabetes

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Abstract

Aim Despite the widespread assumption that adherence drives glycaemic control, there is little published support for this in Type 2 diabetes. The study objective was to determine whether self-reported medication adherence predicts future glycaemic control in Type 2 diabetes, after accounting for baseline control.

Methods Medication adherence (4-item Morisky scale), glycaemic control (HbA₁c%), and other variables were assessed in 287 adult primary care patients prescribed oral medication (40% also on insulin) for Type 2 diabetes. Glycaemic control was reassessed 6 months later. Regression analyses examined concurrent and future glycaemic control as a function of baseline medication adherence after adjustment for baseline glycaemia and other potential confounders.

Results Only half of patients reported high adherence. Cross-sectional adjusted analysis replicated prior reports of an adherence-HbA₁c association ($P = 0.011$). Even after adjusting for baseline HbA₁c, each one-point increase in baseline Morisky total score was associated with a 1.8 mmol/mol (or 0.16%) increase in HbA₁c measured 6 months later. Additionally, baseline endorsement of forgetting to take medication was associated with a 4.7 mmol/mol (or 0.43%) increase in 6-month HbA₁c ($P = 0.005$). This effect persisted after adjusting for psychological distress and did not vary by key demographic and medical features.

Conclusions Even after stringent adjustment for baseline glycaemic control, self-reported adherence to diabetes medication predicts long-term glycaemic control. The Morisky scale is an easy-to-use clinical tool to identify patients whose glycaemic control will subsequently worsen, regardless of age, gender and psychological distress.


Introduction

Although a variety of medications improve glycaemic control in patients with Type 2 diabetes, adherence to insulin and oral hypoglycaemic agents is often suboptimal [1]. Furthermore, it remains somewhat unclear whether medication adherence reliably predicts glycaemic control in Type 2 diabetes [2].

Of eight studies that measured adherence by calculating medication possession ratio from pharmacy refill databases, seven supported an association with subsequent glycated haemoglobin (HbA₁c) [3–9] and one did not [10]. However, while pharmacy-based measures are sensitive and specific for the detection of gross non-adherence, they merely indicate the ceiling of adherence rather than true adherence itself. Therefore, they overestimate adherence among patients who take some but not all of their medication, and among those who do not take their medication on time. Some patients `stockpile' medications by filling their prescriptions on time without actually using all of their medication. This measurement problem is compounded by the now widespread availability (in the USA) of automated refills delivered by mail, through which medication possession is driven by the passage of time rather than by actual medication consumption. Further bias may be introduced because refill intervals can vary several months between different pharmacies and third-party payers. This variation, as well as low-cost medication purchases from some national chain stores, is not captured in most databases. Inaccuracies also arise because of prescribers' ongoing regimen adjustments and the obvious mismatch with sliding scale regimens.

Almost all other adherence-HbA₁c studies relied upon self-reported adherence. While their results generally indicate an association between adherence and HbA₁c [11–15], these
studies are virtually all cross-sectional. Because self-reported adherence could be biased by patients’ foreknowledge of their laboratory results, these studies may overestimate the association. Additionally, if cross-sectional associations do not endure over time, then they are probably clinically unimportant. In the single existing longitudinal study [16], clinical records at a specialty diabetes centre were reviewed over 1 year to assess adherence. Clinician-estimated adherence averaged 80–82% and predicted HbA1c at the end of the year. However, clinician estimates have a poor correlation with adherence data collected from other sources [17] and the non-standardized adherence measure was likely biased by clinicians’ awareness of patients’ HbA1c.

The goal of this study was to clarify the association between self-reported medication adherence and glycaemic control in Type 2 diabetes, using a standardized behavioural assessment applied to a sample of primary care patients. Because the preponderance of cross-sectional data support this association, we hypothesized that adherence predicts glycaemic control 6 months later, even after stringently adjusting for baseline HbA1c level.

Subjects and methods

Participants
Potential participants were identified from the administrative and clinical databases of a large Midwestern urban healthcare system. Eligible patients had Type 2 diabetes as indicated by either: (1) at least one hospitalization with a diabetes–related International Classification of Diseases (ICD)-9 code (250.x, 357.2, 362.0 or 366.41) or (2) at least two outpatient visits with a diabetes–related ICD–9 code, or at least one prescription for an oral glucose control medication, insulin or monitoring supplies. Type 1 diabetes was further ruled out by telephone screening. Participants also were required to be between 18 and 80 years of age and able to complete self-report instruments.

Procedures
The research procedure was pre-approved by our Institutional Review Board (research ethics committee). Eligible patients were mailed a study invitation, which was followed by a telephone call for screening and enrollment. After informed consent, participants attended research appointments at baseline and 6 months later for assessment of adherence, glycaemic control and other variables.

Measures
Medication adherence was assessed using the Morisky scale, a well-validated instrument that elicits information on non-adherence attributable to forgetting, carelessness, feeling better and feeling worse [18]. Each item in the scale has a no/yes format, with a maximum possible score of 4 reflecting worst possible adherence. Across numerous chronic diseases, the scale has shown concurrent and predictive validity, as well as internal consistency [18]. In Type 2 diabetes, it has demonstrated good reliability and predictive validity, and its scores are associated with increased HbA1c.[11]. Glycaemic control (HbA1c) was measured with the DCA 2000 (GMI Inc., Ramsey, MN, USA; normal range 20–42 mmol/mol (4.0–6.0%)), which analyses capillary blood samples through a monoclonal antibody method. Co-morbid medical illnesses were assessed by abstracting electronic medical records using a checklist of common medical illnesses used in prior primary care research (asthma, chronic obstructive lung disease, congestive heart failure, osteoarthritis, rheumatoid arthritis, arthritis associated with lupus or scleroderma, peripheral vascular disease, cirrhosis, chronic hepatitis, coronary artery disease, thyroid disease, Addison’s disease and Cushing’s syndrome) [19,20]. Presence of diabetes complications was measured using a standard self-report checklist of visual, cardiovascular, kidney, genitourinary and other common diabetes complications taken from the Diabetes Care Profile [21]. Diabetes-related distress was measured using the Problem Areas in Diabetes (PAID) scale [22] and depressive symptoms were assessed with the Patient Health Questionnaire-9, (PHQ-9) [23]. Participants classified themselves using US census racial/ethnic categories. Socio-economic status was assessed using the US Census Bureau Index of Socioeconomic Status adjusted for the regional Consumer Price Index [24].

Data analysis
Data were analysed using Stata 11.2 software (StataCorp, College Station, TX, USA). Descriptive analyses were conducted to characterize the sample and distributions were visually and quantitatively examined for violations of statistical assumptions. A matrix of zero-order Pearson correlations was examined to identify bivariate relationships between glycaemic control and its potential demographic and medical confounders, using the criterion of two-tailed P < 0.05. The relationship between adherence and glycaemic control was analysed using ordinary least-squares regression for the prediction of 6-month glycaemic control before and after adjusting models for baseline HbA1c values and other covariates. Standardized beta coefficients (β) were estimated and, again, the P < 0.05 criterion was used to judge statistical significance.

Results
Enrolment and retention
Of 420 patients screened by telephone, 332 met entry criteria, 287 (86%) of whom consented and provided baseline data. Consent was unrelated to age and gender, although African-Americans were more likely to consent
than Caucasians (62 vs. 52%, \( P = 0.025 \)). Thirty-four participants (12%) dropped out after baseline, leaving 253 study completers. Attrition was significantly associated with being under 60 years of age (85% of dropouts vs. 74% of non-dropouts, \( P < 0.014 \)) and being African-American (74 vs. 55%, \( P = 0.036 \)), but was not significantly related to gender, socio-economic status, medication adherence or poor glycaemic control.

Sample characteristics

The sample was demographically and medically diverse (Table 1). Almost half of participants were women and 57% were African-American. Age range was from 27 to 88 years (mean 56.4 ± 8.7) and, as previously reported, was positively correlated with adherence \((r = 0.15, P = 0.012)\) [25]. Socio-economic status was distributed across its entire range and in approximate agreement with expected levels, except for a possible shift from the ‘upper-middle’ into the ‘middle’ strata. Baseline HbA1c was generally elevated [mean 60 ± 19 mmol/mol (7.7 ± 1.7% units); 59% with HbA1c ≥ 53 mmol/mol (or above 7.0%)], 40% were prescribed insulin in addition to an oral hypoglycaemic agent, diabetes duration ranged from 1 to 60 years, complications were common and 20% had at least two significant co-morbid medical conditions. Based upon Morisky scores, 51% of patients could be classified with high adherence (score of 0), 42% with medium adherence (score of 1–2) and 7% with low adherence (score of 3–4). Item-level responses indicated that the most frequently endorsed reasons for non-adherence were forgetting (39%) and carelessness (25%).

**Table 1** Characteristics of baseline sample (\( n = 287 \))

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD or %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>56.4 ± 8.7</td>
</tr>
<tr>
<td>Female gender</td>
<td>48</td>
</tr>
<tr>
<td>African-American ethnicity</td>
<td>57</td>
</tr>
<tr>
<td>Socio-economic status index*</td>
<td>64.8 ± 17.7</td>
</tr>
<tr>
<td>Social stratum</td>
<td></td>
</tr>
<tr>
<td>Upper</td>
<td>12</td>
</tr>
<tr>
<td>Upper–middle</td>
<td>10</td>
</tr>
<tr>
<td>Middle</td>
<td>64</td>
</tr>
<tr>
<td>Lower–middle†</td>
<td>14</td>
</tr>
<tr>
<td>Elevated glyated haemoglobin [IFCC mmol/mol (DCCT%)]†‡</td>
<td>60 ± 19 (7.7 ± 1.7)</td>
</tr>
<tr>
<td>HbA1c ≥ 53 mmol/mol (7.0%)</td>
<td>59</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>10.8 ± 8.0</td>
</tr>
<tr>
<td>Number of diabetes complications</td>
<td>4.3 ± 1.1</td>
</tr>
<tr>
<td>Prescribed insulin in addition to</td>
<td>40</td>
</tr>
<tr>
<td>oral hypoglycaemic agents</td>
<td></td>
</tr>
<tr>
<td>Two or more co-morbid medical conditions</td>
<td>20</td>
</tr>
<tr>
<td>Medication adherence§</td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td></td>
</tr>
<tr>
<td>High (0)</td>
<td>51</td>
</tr>
<tr>
<td>Medium (1–2)</td>
<td>42</td>
</tr>
<tr>
<td>Low (3–4)</td>
<td>7</td>
</tr>
<tr>
<td>Individual items§</td>
<td></td>
</tr>
<tr>
<td>1. Forget to take</td>
<td>39</td>
</tr>
<tr>
<td>2. Careless at times</td>
<td>25</td>
</tr>
<tr>
<td>3. Sometimes stop taking when</td>
<td>7</td>
</tr>
<tr>
<td>feel better</td>
<td></td>
</tr>
<tr>
<td>4. Sometimes stop taking if you feel worse</td>
<td>8</td>
</tr>
</tbody>
</table>

*US Census Bureau Index of Socioeconomic Status, adjusted for current inflation and regional Consumer Price Index.
†Scoring instructions do not distinguish between lower–middle and lower strata.
‡IFCC mmol/mol (DCCT%); normal range: 20–42 mmol/mol (4.0–6.0%).
§Morisky medication adherence scale; higher scores reflect worse adherence.
¶Percentages are given for the response of ‘yes’, which reflects worse adherence.
DCCT, Diabetes Control and Complications Trial; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine.

Bivariate associations

Preliminary bivariate analysis indicated that poor baseline glycaemic control was associated with being younger \((r = 0.30, P < 0.001)\), male \((r = 0.16, P = 0.006)\), African-American \((r = 0.16, P = 0.006)\) and on insulin \((r = 0.16, P = 0.006)\), as well as having fewer co-morbid medical conditions \((r = 0.17, P = 0.005)\). These variables were therefore selected as control covariates for subsequent analyses. Because socio-economic status was not significantly related to either adherence or glycaemic control \((P = 0.468 and 0.606, respectively)\), it was not selected as a covariate.

Concurrent analyses of baseline glycaemic control

We used multiple regression analyses to evaluate the association between medication adherence and concurrent glycaemic control. Medication adherence had a significant zero-order (unadjusted) association with baseline glycaemic control \((\beta = 0.21, P = 0.001)\). This effect remained statistically significant after adjusting for the demographic and medical confounders that were identified above (see Table 2, upper panel; \(\beta = 0.14, P = 0.011\)). In order to identify specific adherence item(s) to analyse, glycaemic control was simultaneously regressed on all four Morisky scale items and the above covariates. Only item 1 was a significant predictor \((P = 0.023)\). When substituted for the Morisky total in the above model, item 1 likewise predicted concurrent glycaemic control \((\beta = 0.13, P = 0.018)\).

Longitudinal analyses predicting glycaemic control

Parallel linear regression models were developed to evaluate the association between medication adherence at baseline and glycaemic control 6 months later, before and after adjusting for confounders and baseline glycaemic control (see Table 2, lower panel). Medication adherence had a zero-order association with future glycaemic control \((\beta = 0.25, P < 0.001)\), which persisted when the model included...
4.7 mmol/mol (or 0.43% unit) increase in HbA1c. Both fully
an affirmative response to item 1 was associated with a
association with glycaemic control (both
However, neither distress variable had a significant unique
symptoms) reduced the effect of medication adherence.
yses explored whether further adjustment for baseline psy-
adherence categorized as high vs. medium or low. Again,
similar findings emerged when adherence and glycaemic
functions (all
potential confounders (β = 0.19, P = 0.003), as well as
baseline glycaemic control (β = 0.09, P = 0.025). The
unstandardized beta coefficient for adherence indicated that
each unit increase in Morisky score (range 0–4) was
associated with a 1.8 mmol/mol (or 0.16% unit) increase
in HbA1c. Finally, when Morisky scale item 1 was substi-
tuted for the total score in the fully adjusted model, it
similarly predicted glycaemic control (β = 0.12, P = 0.005).
An affirmative response to item 1 was associated with a
4.7 mmol/mol (or 0.43% unit) increase in HbA1c. Both fully
adjusted models explained 63% of the variance in 6-month
glycaemic control (P < 0.001).

**Post hoc analyses**

As is often the case, Morisky and HbA1c score distributions
were somewhat skewed in the positive direction. However,
similar findings emerged when adherence and glycaemic
control data were transformed using either log or rank
functions (all P < 0.013). Because the adherence data could
be considered ordinal, analyses were also repeated, with
adherence categorized as high vs. medium or low. Again,
identical results were obtained (P = 0.037). Additional anal-
yses explored whether further adjustment for baseline psy-
chological distress (diabetes-specific distress and depressive
symptoms) reduced the effect of medication adherence.
However, neither distress variable had a significant unique
association with glycaemic control (both P > 0.254), whereas
the effect of medication adherence remained statistically
significant (P = 0.018) after distress measures were included
in the model. Analyses were also conducted to examine
whether medication adherence interacted with any of the
baseline variables, which would indicate whether the effect
of medication adherence on metabolic control was concentrated
within any identifiable subgroup of patients. However,
médication adherence did not significantly interact with age,
gender, ethnicity or co-morbid medical conditions (P > 0.351
for all interaction terms). There was no indication that the
longitudinal association between adherence and 6-month
HbA1c levels differed between patients who did and did not
use insulin (P = 0.308). Adherence similarly did not interact
with having a baseline elevation of either diabetes-related
distress (P = 0.535) or depressive symptoms (P = 0.876).

**Discussion**

To summarize the results, self-reported medication adher-
ence was suboptimal for 49% of primary care patients with
Type 2 diabetes prescribed either oral medication alone or
with insulin. The most frequently endorsed reasons for non-
adherence were forgetting (39%) and carelessness (25%).
Overall adherence and non-adherence attributable to forget-
ting were each significantly associated with concurrent and
subsequent glycaemic control. These associations, previously
reported only in cross-sectional studies, appear to persist for
at least 6 months. Both the concurrent and longitudinal

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**Table 2** Results of regression analyses of concurrent and future glycaemic control

<table>
<thead>
<tr>
<th>Outcome (n)</th>
<th>Baseline predictors</th>
<th>Adjusted for demographic and medical confounders only</th>
<th>Adjusted for confounders and baseline HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>b</td>
<td>β</td>
<td>P</td>
</tr>
<tr>
<td>Baseline HbA1c* (n = 287)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.62</td>
<td>-0.28</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Female gender</td>
<td>-5.24</td>
<td>-0.14</td>
<td>0.011</td>
</tr>
<tr>
<td>African-American ethnicity</td>
<td>3.63</td>
<td>0.10</td>
<td>0.090</td>
</tr>
<tr>
<td>Prescribed insulin</td>
<td>4.58</td>
<td>0.12</td>
<td>0.033</td>
</tr>
<tr>
<td>Co-morbid medical conditions†</td>
<td>-1.33</td>
<td>-0.06</td>
<td>0.383</td>
</tr>
<tr>
<td>Medication adherence total‡</td>
<td>2.63</td>
<td>0.14</td>
<td>0.011</td>
</tr>
<tr>
<td>Non-adherence attributable to forgetting‡‡</td>
<td>5.07</td>
<td>0.15</td>
<td>0.015</td>
</tr>
<tr>
<td>Month 6 HbA1c* (n = 253)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.54</td>
<td>-0.23</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Female gender</td>
<td>-0.28</td>
<td>-0.01</td>
<td>0.904</td>
</tr>
<tr>
<td>African-American ethnicity</td>
<td>4.36</td>
<td>0.11</td>
<td>0.074</td>
</tr>
<tr>
<td>Prescribed insulin</td>
<td>3.35</td>
<td>0.09</td>
<td>0.160</td>
</tr>
<tr>
<td>Co-morbid medical conditions†</td>
<td>-0.83</td>
<td>-0.03</td>
<td>0.602</td>
</tr>
<tr>
<td>Baseline HbA1c*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication adherence total‡</td>
<td>3.58</td>
<td>0.19</td>
<td>0.003</td>
</tr>
<tr>
<td>Non-adherence attributable to forgetting‡‡</td>
<td>9.00</td>
<td>0.23</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*In International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) (mmol/mol) units; analysis of HbA1c% would change unstandardized beta estimates (b), but standardized betas (β) and P levels would not change.
†Coded as 0, 1, ≥ 2.
‡Morisky scale continuous total score (higher scores reflect worse adherence).
§Evaluated without the other adherence score in the model. Covariate effects were estimated with only the Morisky total score in the model and did not change appreciably when item 1 was substituted.
¶Morisky scale item 1: (forget to take; ‘yes’ = 1).

Bold font indicates statistically-significant associations.
associations are independent of key demographic and medical factors such as age, gender, ethnicity, insulin use, medical co-morbidity and baseline glycaemic control. Further adjustment for both diabetes-specific distress and depressive symptoms did not attenuate the effect, and exploratory interaction analysis suggested that the effect is constant across major demographic categories, the presence of diabetes complications and the use of insulin. Therefore, a simple-to-administer self-report measure has considerable practical prognostic value across a variety of patient characteristics.

We believe that ours is the first longitudinal study of self-reported adherence and glycaemic control in Type 2 diabetes, although Type 1 diabetes has been more thoroughly investigated in this regard. As such, this report confirms and significantly extends existing conclusions drawn from cross-sectional and refill-based study designs. Because the Morisky adherence measure does not estimate the percentage of medication doses taken as directed, the results cannot be meaningfully compared with refill-based studies. Notwithstanding, only half of patients reported being highly adherent, with the majority of the remainder emerging as moderately adherent. Because self-report generally tends to yield inflated adherence estimates, actual medication adherence was probably somewhat lower than we observed.

The findings also highlight the predictive validity of self-reported adherence. In psychometric terms, predictive validity is the extent to which test scores predict performance on a relevant future criterion and, as such, it is a more stringent psychometric characteristic than concurrent validity. In this study, each one unit increase in Morisky score (range 0–4) was associated with a 1.8 mmol/mol (0.16% unit) increase in HbA1c, which is approximately twice the effect size reported in an earlier study of Morisky scores and concurrent HbA1c (11). Likewise, reported difficulty remembering to take medication was associated with a 4.7 mmol/mol (0.43% unit) increase in HbA1c. These findings are important because self-report has been criticized as an excessively subjective and upwardly-biased approach to estimating regimen adherence. Because refill-based adherence estimates can also be problematic because of the increased use of lengthy refill intervals and difficulty applying to sliding scale insulin regimens, self-reported diabetes regimen adherence using a standardized scale represents a valid and practical method for use in research and clinical settings.

No interactions with medication adherence were detected. That is, adherence effects are constant across demographic and medical strata defined by age, gender, ethnicity, insulin use and medical co-morbidity. Lack of interaction with distress furthermore suggests that the longitudinal effects of adherence are not concentrated among patients with either diabetes-related distress or depressive symptoms, despite recent findings that depression–glycaemia associations are concentrated among insulin users [26,27]. In other words, the clinical usefulness of Morisky scores seems to generalize across numerous patient characteristics.

Study limitations
While the longitudinal design enabled us to address several alternative explanations, this study was fundamentally naturalistic, which led to some multi-collinearity among the predictors. Although we reported both unadjusted and adjusted estimates so that readers may compare them, randomization to standardized conditions would have more completely controlled this. We considered only medication adherence, whereas adherence to other aspects of the diabetes diet, physical activity and blood glucose self-monitoring are also important and should be assessed in future studies. Although the Morisky measure covers oral medications as well as insulin, it is impossible to isolate adherence to either medication among patients who use both and it does not measure proportion of medication taken. As with medication possession indices, self-report may lead to inflated estimates. However, Morisky scores were validated against medication refill data [28,29] and correlate with concurrent metabolic control [11]. Although attrition was higher among younger and African-American patients, these groups remained well represented and the data analyses adjusted for these characteristics. Because we oversampled African-Americans, the findings may not generalize to all Caucasian or Latino/Hispanic patients. Arguing against this possibility, no interactions with ethnicity or other demographic variables were detected and demographic variance was accounted for. While the current study extends the evidence base to include relationships with glycaemic control over time, future studies should replicate and extend this inquiry across a longer period of time. Although little support was found for potential statistical interactions and other alternative explanations, statistical power to detect these effects may have been limited by the inclusion of additional main effect and interaction terms in the model.

Clinical implications
The findings imply that poor adherence is influential enough to affect future glycaemic control, regardless of current control. This impact is greater than that of either diabetes-specific or generalized psychological distress, implying that adherence is a key issue even among non-distressed patients. Clinical efforts to improve glycaemic control thus should emphasize medication-taking regardless of whether or not there is a need for distress alleviation. While our item-level results suggest that the most important adherence strategies will be those that directly reduce forgetting, such as automated reminders [31], regimen simplification [30] and regimen tailoring [32], additional validated strategies are electronic monitoring [33] and motivational interviewing [34]. Finally, at a practical level, between one and four easy-to-administer questions could be routinely incorporated into clinical diabetes assessments.
when the goal is to achieve or maintain glycaemic control. Caution is warranted, however, because demand characteristics and social desirability bias may affect how even a well-validated research tool performs when it is administered in clinical practice.

Conclusions

Self-reported adherence to Type 2 diabetes medication is robustly associated with glycaemic control 6 months later, even after adjusting for baseline glycaemic control, level of psychological distress, diabetes characteristics and sociodemographic features. Clinicians may be able to use brief self-report measures to efficiently identify those in need of adherence interventions to prevent poor diabetes outcomes.

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Competing interests

None declared.

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References