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Ventricular Arrhythmia-Free Survival Following Therapeutic Hypothermia in Patients with Sudden Cardiac Death Due to Ventricular Tachycardia or Fibrillation

Basil M. Saour¹, Yong H. Ji², Edward F. Philbin¹, Henry T. Tan¹, Duy T. Nguyen³, James J. O’Brien¹, Mandeep S. Sidhu¹, David A. Steckman¹, Mikhail T. Torosoff*¹

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Abstract

Background: The potential benefits of implantable cardioverter-defibrillator (ICD) therapy in patients with sudden cardiac death (SCD) treated with therapeutic hypothermia (TH) have not been well studied. Methods: Incidence of recurrent non-sustained ventricular arrhythmia, ICD therapy, and death were ascertained in 64 consecutive survivors of SCD due to ventricular fibrillation or tachycardia, who were treated with TH. Follow-up was 31.5 ± 3.3 months in 41 ICD recipients and 36.3 ± 3.9 months in 23 patients who did not receive an ICD due to the presence of a reversible cause of cardiac arrest, an acute myocardial infarction in 87%.

Results: Combined incidence of ventricular arrhythmia, ICD therapy, or death in patients who underwent ICD placement (21.9%) were similar to overall mortality in the patients who did not receive an ICD (21.7%, p = 0.752). ICD placement was associated with a significant mortality benefit; 95.1% survival in ICD recipients vs. 78.3% in the no-ICD group (p = 0.038). Electrocardiographic findings of ST segment elevation on admission were associated with increased event rate in ICD recipients (p = 0.039) and increased mortality in SCD patients who did not receive an ICD (p < 0.001). Other studied variables had no significant effect on the investigated outcomes. Conclusions: SCD survivors treated with TH are at increased risk for recurrent arrhythmic events and derive significant mortality benefit from ICD implantation. Increased mortality in revascularized SCD patients with acute coronary syndrome, thought to have a reversible cause of cardiac arrest, calls for prospective trials investigating utility of ICD in this vulnerable patient population.
**Keywords**

Sudden Cardiac Death, Therapeutic Hypothermia, Implantable Cardiac Defibrillator

1. Introduction

Each year there are estimated 325,000 cases of sudden cardiac death (SCD) in the United States [1] and approximately 50 per 100,000 cases world-wide accounting for 15% - 20% of all-cause mortality [2] [3] [4] and for >50% of all coronary heart disease related mortality [1] [5] [6]. Described first in the late 1950s [7] [8] [9], therapeutic hypothermia (TH) in SCD patients has consistently demonstrated a mortality benefit with improved functional status [10]-[17] and has since become the standard of care in patients who experience return of spontaneous circulation [18]. Implantable cardioverter defibrillator (ICD) placement is recommended and performed in SCD survivors with projected life expectancy greater than one year and without a reversible cause for cardiac arrest [19]. However, the landmark secondary SCD prevention ICD trials [20] [21] [22] were performed prior to the advent and widespread utilization of TH and the outcomes associated with ICD implantation in SCD survivors treated with TH have not previously been reported. We investigated the incidence and predictors of recurrent ventricular arrhythmias and mortality, as well as the benefits of ICD placement in SCD survivors treated with TH.

2. Methods

2.1. Patient Population and Study Design

The study cohort consisted of 64 consecutive patients with SCD and the initial rhythm of ventricular fibrillation (VF) or ventricular tachycardia (VT) that underwent TH and survived to hospital discharge at a single tertiary care academic medical center between 2008 and 2013. Patients with less than 1 year life expectancy and/or with Do Not Resuscitate (DNR) status were excluded from the study cohort.

All patients were treated according to the previously described TH protocol with a target temperature 32 - 34 degrees C over a period of 24 hours [10]. After TH, all patients received guideline directed medical therapy, as dictated by the medical condition [19]. All studied patients were considered for ICD implantation, which was performed in qualified subjects according to the published guidelines [19]. The study control group consisted of SCD-TH survivors who did not have an ICD implanted due to what was thought to be an acute reversible event leading to SCD [19].

2.2. Data Collection

The presence of ST segment elevation (STE) on the first recorded electrocardiog-
gram (ECG) after defibrillation was ascertained according to the Third Universal Definition of Myocardial Infarction criteria, as at least 0.1 mV STE 60 - 80 msec after the J point, in two contiguous leads other than V1 and V2 [23]. In patients who underwent coronary angiography, presence of significant obstructive atherosclerotic coronary artery disease (CAD) was defined as one or more epicardial coronary arteries with stenosis of greater or equal to 50% in left main coronary artery or 70% in the left anterior descending, circumflex, or right coronary arteries [24].

Echocardiograms at the time of the index SCD event and at 3 month follow-up were acquired according to the American Society of Echocardiography recommendations [25]. LV systolic function was graded as preserved if EF was greater or equal to 55%. LV systolic dysfunction was graded as mildly reduced if EF was 45% - 54%, moderately reduced if EF was 30% - 44%, and severely reduced if EF was <30% [25].

For patients who had ICDs implanted, frequency and timing of shock (high voltage therapy with defibrillation) or anti-tachycardia pacing (ATP) were determined from serial ICD transmissions and device interrogations. All tracings were reviewed manually by the Board certified electrophysiologists to exclude episodes of inappropriate shock or ATP for atrial arrhythmias, electrical magnetic interference, myopotentials, lack of lead integrity, and therapy for oversensing.

Two studied endpoints included all-cause mortality and a composite endpoint of mortality and appropriate device therapy (ATP or high voltage therapy with defibrillation) in ICD recipients and, since the arrhythmic events could not be ascertained in SCD-TH survivors who did not have an ICD implanted, mortality alone in the no ICD group. Event rates were compared between SCD-TH survivors who did and did not have an ICD implanted.

Overall mortality and device therapy and arrhythmia-free mortality were assessed at 1-year post discharge and at the end of the follow-up period. Mortality was determined through the medical charts, including the outpatient office follow-up records, and ascertained through the National Death Index. Cause of death was obtained from death certificates and discharge summaries.

This was a retrospective cohort study, which involved no risk for the subjects, with the waiver of informed consent not adversely affecting the rights and welfare of the subjects. The study was approved by the Institutional Review Board.

### 2.3. Statistical Analysis

Continuous data was expressed as means with standard deviations. Differences in continuous variables were assessed with an unpaired t-test and non-parametric Kruskall-Wallis test, when appropriate. Categorical data was expressed as proportions and the differences in proportions were assessed with Fisher’s exact test. Mortality and time to device therapy were analyzed using Kaplan-Meier estimates with Mantel-Cox log-rank test for between group differences.

Variables associated with mortality, defibrillation, or ATP were further sub-
jected to logistic regression analysis. Variables found to be associated with mortality or device therapy in a univariable logistic regression were then retained in the multivariable logistic regression analysis.

In all analyses, \( p \)-value \( \leq 0.05 \) was defined as statistically significant. Based on the previously reported 25% rate of recurrent arrhythmic or death rate in SCD patients (20 - 22) and the Type I error probability of 0.05, the study consisting of 41 ICD recipients and 23 control patients had power of 0.348 to detect a 25% absolute difference in outcomes and power of 0.958 to detect a 50% absolute difference. Analysis was performed using commercially available statistical software (SAS Institute Inc., Cary, NC, 2007).

3. Results

The study cohort consisted of 64 consecutive SCD patients with cardiac arrest due to ventricular tachycardia or fibrillation, who were treated with therapeutic hypothermia and survived to hospital discharge. Median follow-up length was 31.5 +/- 3.3 months in the ICD group and 36.3 +/- 3.9 months in the no-ICD group. Of the 23 patients in the no-ICD arm, an ICD was not implanted in 2 patients with hyperkalemia and in 1 patient with prolonged QT on presentation, which re-solved with correction of electrolytes and outpatient drug discontinuation respectively. An ICD was also not implanted in an additional 20 patients who were presumed to have an acute ischemic event leading to SCD and did not meet MUSTT criteria [26].

Coronary angiography was performed in 59 patients, and 43 were found to have obstructive CAD which required revascularization in 67.4% (29/43). Of 10 patients who underwent coronary artery bypass grafting, 5 received ICD (50%); of 19 patients who underwent percutaneous coronary intervention, 8 received an ICD (42%, \( p = 0.241 \)). Patients with obstructive CAD or ST elevations were significantly less likely to receive an ICD (54.5% vs. 85% in patients without ST elevation or obstructive CAD, \( p = 0.019 \)). Otherwise, there were no significant differences, including initial or follow-up evaluation of systolic function as evidenced by the LV ejection fraction (EF), between the patients who did or did not receive an ICD (Table 1). Ten patients presented with ST elevation and all were subsequently found to have obstructive coronary disease. Obstructive coronary artery disease was also found in 33 of 49 patients who presented without ST elevation.

A total of 7 patients expired during the follow-up period, 2 with and 5 without ICD implantation. Of those without an ICD, four patients died of cardiac arrest; other causes of death were intracranial hemorrhage, pneumonia, and congestive heart failure. Of the 2 expired patients with ICD implantation, one died from cardiopulmonary arrest and the other from heart failure.

During the specified follow-up period, appropriate ICD therapy occurred in 7 patients (Table 1). Non-sustained ventricular tachycardia (NSVT) which did not require device therapy was noted in 2 additional patients. None of the baseline parameters, distinguished SCD-TH survivors who required appropriate device
therapy after the hospital discharge (*Table 1*) from those patients who did not, including reduced EF (*p* = 0.282) or significant obstructive coronary artery disease (*p* = 0.839).

All recorded follow-up deaths occurred within 24 months from the index event hospitalization (*Figure 1*). ICD placement was associated with a trend towards improved 1 year survival, which was found to be significant at the end of 2.5 year follow-up (*p* = 0.038, *Table 2*, and log-rank *p* = 0.05, *Figure 1(a)*). Advanced age (*p* = 0.044) and ST elevation on admission (*p* < 0.001) were associated with decreased survival (*Table 2*). In multivariable logistic regression analysis including age, ejection fraction < 35%, and ICD status, only ST elevation for cardiac arrest was associated with decreased survival (*Table 3*, log-rank *p* = 0.011, *Figure 1(b)*).

There was no difference in EF between patients who presented with ST eleva-

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**Table 1.** Factors associated with ICD implantation and subsequent device therapy.

<table>
<thead>
<tr>
<th>Category</th>
<th>No-ICD vs. ICD Comparison</th>
<th>ICD Rx vs. ICD No-Rx and vs. No-ICD Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No-ICD N = 23</td>
<td>ICD N = 41</td>
</tr>
<tr>
<td>Age (years old)</td>
<td>60 (15.3)</td>
<td>58.1 (13.4)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81 (15.5)</td>
<td>87.0 (23.3)</td>
</tr>
<tr>
<td>Gender, Females</td>
<td>3 (13)</td>
<td>9 (22)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>117 (43.5)</td>
<td>126.6 (29.7)</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>87.3 (26.8)</td>
<td>85.3 (16.6)</td>
</tr>
<tr>
<td>Ejection Fraction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35%</td>
<td>6 (26.1)</td>
<td>16 (39)</td>
</tr>
<tr>
<td>35% - 39%</td>
<td>4 (17.4)</td>
<td>7 (17.1)</td>
</tr>
<tr>
<td>40% - 54%</td>
<td>1 (4.3)</td>
<td>2 (4.9)</td>
</tr>
<tr>
<td>&gt;54%</td>
<td>12 (52.1)</td>
<td>16 (39)</td>
</tr>
<tr>
<td>ST Elevation</td>
<td>7 (30.4)</td>
<td>4 (9.8)</td>
</tr>
<tr>
<td>K (mg/dL)</td>
<td>3.6 (0.7)</td>
<td>4.1 (1.1)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.6 (1.1)</td>
<td>1.9 (2.3)</td>
</tr>
<tr>
<td>pH (units)</td>
<td>7.27 (0.148)</td>
<td>7.244 (0.124)</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>195.4 (53.8)</td>
<td>227.3 (115.0)</td>
</tr>
<tr>
<td>Ca (mg/dL)</td>
<td>8.2 (0.8)</td>
<td>8.2 (0.70)</td>
</tr>
<tr>
<td>Mg (mg/dL)</td>
<td>1.9 (0.30)</td>
<td>2.0 (0.4)</td>
</tr>
<tr>
<td>Hemoglobin (mg/dL)</td>
<td>13.5 (1.8)</td>
<td>13.5 (1.9)</td>
</tr>
<tr>
<td>Hematocrit (units)</td>
<td>40.3 (5)</td>
<td>39.8 (5.7)</td>
</tr>
<tr>
<td>Obstructive CAD</td>
<td>20/21 (95.2%)</td>
<td>23/38 (60.5%)</td>
</tr>
<tr>
<td>Alive at 1 year</td>
<td>20 (86.9%)</td>
<td>39 (95.1%)</td>
</tr>
<tr>
<td>Alive at 2.5 years</td>
<td>18 (78.3%)</td>
<td>39 (95.1%)</td>
</tr>
</tbody>
</table>

Numbers represent means (SD) or absolute counts (%).
Figure 1. Kaplan Meier survival estimates. (a) Long-term survival in SCD patients treated with therapeutic hypothermia, stratified by ICD status; (b) Long-term survival in SCD patients treated with therapeutic hypothermia, stratified by ST elevation on admission. ICD placement was associated with improved long-term survival. Admission ST elevation (STE) was associated with decreased long-term survival.

Table 2. Factors affecting follow-up survival.

<table>
<thead>
<tr>
<th>Category</th>
<th>1 year follow up</th>
<th></th>
<th>P-value</th>
<th>1 year follow up</th>
<th></th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alive N = 59</td>
<td>Expired N = 5</td>
<td>P-value</td>
<td>Alive N = 57</td>
<td>Expired N = 7</td>
<td>P-value</td>
</tr>
<tr>
<td>Age (years old)</td>
<td>57.9 (14.0)</td>
<td>68.8 (11.1)</td>
<td>0.0974</td>
<td>57.6 (13.7)</td>
<td>68.9 (13.4)</td>
<td>0.044</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>85.6 (21.3)</td>
<td>76.0 (14.2)</td>
<td>0.324</td>
<td>86.5 (21.1)</td>
<td>71.7 (13.9)</td>
<td>0.077</td>
</tr>
<tr>
<td>Gender, Females</td>
<td>12 (20.3)</td>
<td>0 (0)</td>
<td>0.263</td>
<td>12 (21.1)</td>
<td>0 (0)</td>
<td>0.178</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>122.8 (35.3)</td>
<td>128.6 (35.1)</td>
<td>0.724</td>
<td>123.0 (36.0)</td>
<td>125.1 (29.3)</td>
<td>0.879</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>85.8 (19.0)</td>
<td>87.8 (37.8)</td>
<td>0.839</td>
<td>85.7 (18.9)</td>
<td>88.1 (33.1)</td>
<td>0.771</td>
</tr>
<tr>
<td>Ejection Fraction &lt;35%</td>
<td>20 (33.9)</td>
<td>2 (40)</td>
<td>0.197</td>
<td>20 (35.1)</td>
<td>2 (28.6)</td>
<td>0.287</td>
</tr>
<tr>
<td>35% - 39%</td>
<td>11 (18.6)</td>
<td>0 (0)</td>
<td>0.197</td>
<td>11 (19.3)</td>
<td>0 (0)</td>
<td>0.087</td>
</tr>
<tr>
<td>40% - 54%</td>
<td>2 (3.4)</td>
<td>1 (20)</td>
<td>0.451</td>
<td>2 (3.5)</td>
<td>1 (14.3)</td>
<td>0.451</td>
</tr>
<tr>
<td>&gt;54%</td>
<td>26 (44.1)</td>
<td>2 (40)</td>
<td>0.925</td>
<td>24 (42.1)</td>
<td>4 (57.1)</td>
<td>0.873</td>
</tr>
<tr>
<td>ST Elevation</td>
<td>6 (10.2)</td>
<td>5 (100)</td>
<td>0.0001</td>
<td>6 (10.5)</td>
<td>5 (71.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>K (mg/dL)</td>
<td>3.9 (1.9)</td>
<td>3.9 (0.3)</td>
<td>3.9 (1.1)</td>
<td>3.8 (0.4)</td>
<td>3.8 (0.4)</td>
<td>0.873</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.8 (2.1)</td>
<td>1.5 (0.4)</td>
<td>0.868</td>
<td>1.8 (2.1)</td>
<td>2 (1.4)</td>
<td>0.806</td>
</tr>
<tr>
<td>pH (units)</td>
<td>7.255 (0.131)</td>
<td>7.235 (0.160)</td>
<td>0.777</td>
<td>7.246 (0.123)</td>
<td>7.318 (0.201)</td>
<td>0.206</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>219.6 (101.2)</td>
<td>176.6 (55.3)</td>
<td>0.355</td>
<td>221.9 (102.1)</td>
<td>169.9 (48.8)</td>
<td>0.19</td>
</tr>
<tr>
<td>Ca (mg/dL)</td>
<td>8.2 (0.7)</td>
<td>8.5 (0.3)</td>
<td>0.451</td>
<td>8.2 (0.7)</td>
<td>8.4 (1.1)</td>
<td>0.45</td>
</tr>
<tr>
<td>Mg (mg/dL)</td>
<td>2 (0.3)</td>
<td>2.1 (0.2)</td>
<td>0.468</td>
<td>2 (0.4)</td>
<td>2.1 (0.2)</td>
<td>0.513</td>
</tr>
<tr>
<td>Hemoglobin (mg/dL)</td>
<td>13.6 (1.9)</td>
<td>12.7 (1.4)</td>
<td>0.302</td>
<td>13.7 (1.9)</td>
<td>12.4 (1.3)</td>
<td>0.101</td>
</tr>
<tr>
<td>Hematocrit (units)</td>
<td>40.1 (5.6)</td>
<td>38.6 (4.6)</td>
<td>0.0558</td>
<td>40.3 (5.6)</td>
<td>37.9 (4.0)</td>
<td>0.284</td>
</tr>
<tr>
<td>Obstructive CAD</td>
<td>39/55 (70.9%)</td>
<td>4/4 (100%)</td>
<td>0.206</td>
<td>39/54 (72.2%)</td>
<td>4/5 (80%)</td>
<td>0.708</td>
</tr>
<tr>
<td>ICD</td>
<td>39/59 (66.1%)</td>
<td>2/5 (40)</td>
<td>0.243</td>
<td>39/57 (68.4%)</td>
<td>2/7 (28.6%)</td>
<td>0.038</td>
</tr>
</tbody>
</table>

Numbers represent means (SD) or absolute counts (%).
Table 3. Logistic regression analysis of the survival predictors.

<table>
<thead>
<tr>
<th>Category</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exp (Coef)</td>
<td>95% Confidence Intervals</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (Per Year)</td>
<td>0.928</td>
<td>0.862 - 0.999</td>
</tr>
<tr>
<td>EF &lt; 35%</td>
<td>0.740</td>
<td>0.131 - 4.165</td>
</tr>
<tr>
<td>ST Elevation</td>
<td>0.047</td>
<td>0.007 - 0.298</td>
</tr>
<tr>
<td>ICD</td>
<td>5.417</td>
<td>0.958 - 30.630</td>
</tr>
</tbody>
</table>

tions vs. those without ST segment elevation (p = 0.485). Likewise, a reduced LVEF was not predictive of decreased survival (Table 2). Of the expired ICD recipients, one had an LVEF of 40% - 49% and another one had an LVEF < 35%. Of the 5 expired patients in the no-ICD group, 4 had an LVEF > 50%, and only one patient had an LVEF of < 35%, a non-significant difference (p = 0.287, when compared to ICD group).

Incidence of arrhythmic event or death, an arrhythmia-free survival, in ICD group was compared to all-cause mortality in patients who did not receive an ICD (Figure 2). There were a total of 9 events (21.9%) in the ICD group and 5 events (21.7%) in the no-ICD group, a non-significant difference (log-rank p = 0.752, Figure 2(a)). In both the ICD and no-ICD groups, ST elevation on admission was associated with decreased arrhythmia-free survival (log-rank p = 0.039, Figure 2(b)).

4. Discussion

Therapeutic hypothermia (TH) has consistently demonstrated a mortality benefit with improved functional status [10]-[17] and it is widely implemented in SCD patients who experience return of spontaneous circulation [18]. We have conducted a retrospective cohort study of patients with SCD due to ventricular fibrillation or tachycardia, who were treated with TH (VT-VF SCD-TH) and subsequently underwent an ICD placement according to the current standard of care based on the landmark secondary SCD prevention ICD trials, the Cardiac Arrest Study Hamburg (CASH) [21], the Canadian Implantable Defibrillator Study (CIDS) [22], and The Antiarrhythmics versus Implantable Defibrillators (AVID) trials [20]. However, these landmark secondary SCD were performed prior to the advent and widespread utilization of TH, and the outcomes associated with ICD implantation in SCD survivors treated with TH have not previously been reported.

In the studied contemporary cohort of VT-VF SCD-TH patients, ICD placement was associated with a significant improvement in overall survival, while those discharged without an ICD remained at high mortality risk. Reduced LV ejection fraction had no effect on outcomes, mean-while ST segment elevation or obstructive CAD portended a poor prognosis.

The mortality rate of VT-VF SCD-TH survivors was 10.9%, which is better than reported 24% mortality during 2 year follow-up in AVID [20], 21% during
Figure 2. Kaplan Meier time to death or ICD therapy estimates. (a) Arrhythmia-free long-term survival in SCD patients treated with therapeutic hypothermia, stratified by ICD status; (b) Arrhythmia-free long-term survival in SCD patients treated with therapeutic hypothermia, stratified by ST elevation on admission. ICD placement did not affect long-term ICD therapy-free survival. Admission ST elevation (STE) was associated with decreased ICD therapy-free survival.

2 year follow up in CIDS [22], and the 44% rate over 5 years in CASH trials [21]. It is possible that improved survival in VT-VF SCD-TH patients is reflective of the TH benefits [10] [11]. Also, the decreased mortality may be due to consistent utilization of the evidence based modern optimal medical therapy (OMT) in patients with ASCVD, which included beta-adrenergic blockers and angiotensin-converting enzyme inhibitors in all qualifying subjects, which was not used consistently in prior studies [20] [21] [22].

The observed rates of ICD therapy in VT-VF SCD-TH cohort were 14.6% during the first year, and a total of 17.0% by the end of the 2.5 year study follow-up period, an annual device therapy rate of 6.9%. The observed annual device therapy rate in VT-VF SCD-TH patients is comparable to 5% annual event rates reported in primary SCD prevention trials including SCD-HeFT [27] and MADIT II [28]. The device therapy rates were not reported in CASH, CIDS, and AVID trials [20] [21] [22].

A substantial number of VT-VF SCD-TH survivors, 23 of 64 patients in our study, did not undergo ICD implantation due to suspected reversible causes of cardiac arrest. All patients in our study were evaluated prior to discharge for ICD implantation, and neurologic status was specifically addressed; patients with poor neurologic status, DNR/DNI status, and patients with limited life expectancy of <1 year were excluded from the study. The remaining 64 patients included in the study did not have significant neurologic deficits following TH. In our study, the observed annual mortality rate in VT-VF SCD-TH survivors who did not receive an ICD was 8.7%, with more than half of the deaths attributed to cardiac arrest. This mortality rate is comparable to the annual mortality rates noted in the landmark primary SCD prevention trials: 7.2% rate in SCD-HeFT control group [27] and 8.0% rate in MADIT II control group [28]. Our findings suggest that regardless of the ICD allocation, VT-VF SCD-TH patients have sig-
nificantly increased mortality risk, which is mostly due to arrhythmic events, consistent with data from the landmark secondary and primary SCD prevention trials.

Historically, reduced LV systolic function has predicted increased mortality and has been associated with primary prevention benefit in ICD recipients [20] [21] [22]. Effects of LV function on incidence of arrhythmic events/deaths in VT-VF SCD-TH survivors have not previously been well studied. In our investigation, 83.3% of VT-VF SCD-TH treated patients who required ICD therapy had an EF > 35% at the time of the 3 month follow-up evaluation, and only one expired patient had EF < 35%. Of the 10 patients with decreased ejection fraction, who did not attain an ICD prior to discharge, nine presented with ST elevations and one with hyperkalemia which were thought to be the reversible causes of SCD. In all 10 patients subsequent echocardiograms demonstrated LV ejection fraction improvement to >40% at 3-6month follow up intervals. Thus, while surprising, our results indicate that left ventricular systolic dysfunction alone may not be a significant determinant of mortality or future device therapy in VT-VF SCD-TH patients, possibly due to better myocardial salvage and cardio-protective effects of TH noted in the experimental studies [29]. It is possible that patients with significant pre-arrest LV systolic dysfunction were less likely to survive the index event, which has resulted in selection bias towards patients with preserved ejection fraction, thus explaining limited significance of LV dysfunction in predicting cardiac events during follow-up. However, this “selection bias” is not unique to our patients, but is a common attribute in all survivors of sudden cardiac death.

In our study, the evidence of ischemia, defined by ST elevation or significant obstructive CAD, was predictive of adverse outcomes in VT-VF SCD-TH patients, adding to the body of evidence linking ventricular arrhythmias, acute ischemic events, and increased mortality in SCD patients. Ischemia may trigger ventricular tachycardia and, reciprocally, decreased coronary perfusion due to ventricular arrhythmia may progress to transmural ischemia in patients with obstructive coronary artery disease [24] [30]. In fact, late gadolinium enhancement pattern consistent with unidentified prior myocardial infarction has been demonstrated in 58% of SCD survivors with unclear etiology of cardiac arrest [31].

SCD risk stratification strategy in patients with an acute ischemic event is evolving. ICD benefit has been demonstrated in primary SCD prevention trials in patients with acute myocardial infarction and depressed ejection fraction < 35% [32] or when LV ejection fraction < 40% was accompanied by non-sustained ventricular tachycardia and an inducible sustained ventricular tachycardia at the electrophysiologic study [26]. ICD implantation has been associated with improved survival in patients with ejection fraction > 35% who suffered SCD from an ischemic event [33]. However, since acute myocardial ischemia may be a reversible cause of cardiac arrest, SCD treated patients with obstructive CAD or ST elevations are currently not considered for secondary prevention and do
not undergo ICD implantation [19].

In studied SCD survivors treated with therapeutic hypothermia, the mortality rate in patients who did not qualify for ICD placement was similar to a combined device therapy and mortality rate in ICD recipients. This suggests that VT-VF SCD-TH survivors with an ischemic substrate may be at increased risk of recurrent arrhythmic events, despite preserved left ventricular systolic function and improved hospital survival, which is likely associated with benefits of TH [10] [11]. Foregoing ICD implantation in these patients, based on assumption that there was a reversible cause of SCD, may leave them potentially unprotected against future SCD events. The DINAMIT trial of patients after an acute coronary event found that early implantation of ICD was associated with decrease in SCD but no overall mortality benefit [32]. Our study population is very different from DINAMIT in that all of our patients have presented with SCD and were treated with TH; a population that was not represented in significant numbers in the DINAMIT study [32]. The population of SCD-TH survivors regardless of etiology is as yet an unstudied population with respect to randomized clinical trials. Our study indicates that there may be potential mortality benefit in early ICD implantation in survivors of SCD due to ventricular tachycardia or fibrillation, treated with TH; however, this statement of course will require a randomized clinical trial for confirmation.

5. Limitations

We consider our findings to be hypothesis generating and requiring confirmation in prospective trials. This was a single site retrospective study involving a modest number of subjects with an inherent selection bias for patients who are most likely to survive a cardiac arrest due to ventricular fibrillation or tachycardia. Patients who did not survive to hospital admission or passed away during hospitalization represent a different sample of patients; however, because the goal of this trial was to provide insight into the potential role of ICD in VT-VF SCD-TH survivors, looking at only candidates for ICD implantation gives the real world experience, according to the accepted practice patterns. Patients were not randomized to treatment categories; instead, everyone was treated according to the established guidelines, once again, making our findings clinically relevant. Lastly, patients who did not receive an ICD were not prospectively monitored for incidence of arrhythmia; instead, causes of death were ascertained from death certificates and discharge summaries and could not be independently adjudicated. Future studies of similar nature may be conducted with implantable or wearable cardiac telemetry recorders in VT-VF SCD-TH patients who currently do not qualify for ICD placement.

6. Conclusion

To our knowledge, this is the first study specifically investigating outcomes in survivors of sudden cardiac death due to ventricular tachycardia or fibrillation treated with therapeutic hypothermia. We have observed that these SCD patients
are at increased risk of recurrent arrhythmia and derive benefit from ICD implantation comparable to such reported in the landmark secondary SCD prevention trials, which were performed prior to the advent of therapeutic hypothermia. In this patient population, a preserved systolic function does not appear to confer a follow-up survival benefit; however, obstructive coronary artery disease and ST segment elevation at the time of presentation are associated with an increased mortality during a 2.5 year follow-up period. Therefore, the VT-VF SCD-TH survivors with an ischemic substrate appear to be at increased risk of death, likely due to recurrent arrhythmias, and, without an ICD implantation, may be potentially unprotected against future SCD events. Our findings need to be confirmed in a prospective randomized trial designed to evaluate the mortality benefit of ICD implantation after therapeutic hypothermia, including patients with the presumed ischemic etiology of an arrhythmic event. Until further studies, close monitoring for recurrent arrhythmias is imperative in this vulnerable patient population.

References


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Evaluation of an Innovative Diagnostic Method for Detection of Antibodies and Antigens

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Abstract

Reports manifest a continuing need for the development of rapid and on-site (point of care) assays. Current diagnostic methods commonly used for detection of antibodies and antigens have significant limitations. Scientists at Micro Detect, Inc. have developed an innovative diagnostic device (method) that can be utilized broadly for antibody/antigen interactions including diagnostic assays in the medical, veterinary and food industries. The developed device can be utilized for the detection of antibodies against a single antigen or vice versa. It can also be tailored for specific panels that detect antigens or antibodies for diverse infectious agents, proteins, hormones, tumor markers, autoimmun e markers, and allergens. Additionally, it can also be used for detection of toxins, antitoxins, nucleic acids, enzymes, drugs, etc. in both humans and animals. Specimens used in different formats of the device can be tears, saliva, whole blood, serum, plasma, urine, stool, and other bodily discharges. The good intra and inter precisions and acceptable linearity of the device support reliable use of the device. The CV of the device is 1.9% - 2.2%. Likewise, the performance of the device using 92 confirmed negative and positive specimens via a typical assay showed 100% sensitivity, 80% specificity, 96.8% efficacy, 80% positive predictive value, and 100% negative predictive value. The results of our feasibility study suggest reliable utility of a device for rapid, easy-to-use, inexpensive, and on-site (point of care) diagnostic assays. This presents a potential breakthrough in diagnostic methodologies that can be integrated into modern medicine and food industries.

Keywords

Rapid Diagnostic Test, UV Laser Spectroscopy, Panel Antibody/Antigen Assays, Point of Care Testing

1. Introduction

A significant number of diagnostic tests routinely performed in the medical, ve-
terinary and food industries integrate antigen antibody interactions. Routinely, either a specific antibody is used to detect presence of a specific antigen or a specific antigen is used to detect presence of a specific antibody. The diagnostic methods that are implemented include agglutination, western blot, ELISA, RIA, immune diffusion, complement fixation, lateral flow (one-step), and PCR (limited application). Of these methods, ELISA and lateral-flow are the most commonly utilized.

In lateral-flow, which can also be considered as an on-site method delivering rapid results, gold or colored latex particles are coated with specific antigens or antibodies. In a positive specimen, the known antibodies or antigens fixed on a membrane capture corresponding antigens or antibodies coated on the gold or latex particles. Although this method has several limitations and cannot be widely used, for the detection of certain analytes and screening purposes, it remains the best choice. This method has enhanced performance when the detection of an antigen is the aim of the test and when the concentration of detectable antigens or antibodies in the sample is relatively elevated. With lateral-flow, the borderline positive or negative specimens may produce false negative or false positive results. This method is mostly used for the detection of a single analyte. Recently, devices that can measure up to 4 analytes, especially for drugs abuse assays, have been developed.

For certain disease states, measuring the titers of a certain antibody (IgG, IgM, IgA or IgE) in provided patient specimens is integral to monitor disease severity and stage. For this reason, the ELISA method is often the best choice. In ELISA, a known and specific antigen is fixed in the wells of microplates. After addition of a patients’ specimen, addition of the second corresponding anti-antibody conjugate, and addition of the substrate, the titers of the first antibodies in the specimens are measured via ODs using a spectrophotometer. In ELISA, the second antibody is mostly conjugated with an enzyme or a florescent dye. ELISA can be used for measuring the titers of the antibodies in several specimens against a single antigen or for the detection of different antibodies against specific antigens. Performing ELISA assays necessitates skilled technicians and should be done in a clinical laboratory setting. This method consists of several reagents and incubation times, as such, ELISA is not considered as a rapid result test.

The market for rapid medical diagnostic tests (on-site) in the United States was estimated at $19.4 billion in 2014 [1]. The global market for the development of rapid diagnostic methodology has demonstrated accelerated growth over the past few years and this trend is likely to sustain. It is anticipated that the total market in the United States alone will increase to $27 billion by 2020. Considering the global market as well, this number will only exponentially grow [2]. Rapid on-site testing can provide valuable insight for physicians in a multitude of settings by expediting implementation of therapeutic plans. This is a particularly important time for such a breakthrough in diagnostic methodology as the healthcare industry is evolving to leverage escalating costs. The screening of the
infectious agents or their toxins in the food industry is also an expansive market, estimated to have a fiscal burden of $27 billion in 2012 [3].

Development of a fast, on-site, inexpensive, and easy to use diagnostic method has significant promise for both the medical and food industries. Scientists at Micro Detect, Inc. have developed such a method/device (patent pending). The innovative technology, UV Laser Spectroscopy Diagnostic (UVLSD) developed at Micro Detect, Inc. has the ability to readily detect antigens or antibodies from either single or multiple analytes (specific panels). This includes pathogenic infectious agents (viruses, bacteria, fungi, chlamydia, and/or protozoa), antibodies to autoimmune markers, and allergens. It can also be used for detection of toxins, antitoxins, proteins, nucleic acids, enzymes, hormones, tumor markers, and drugs in humans and animals. Likewise, it may be employed for the detection of certain pathogenic microorganisms and/or their toxins in the food industry or plant pathology discipline. The device can also be tailored to measure the presence of specific antibody classes against a specific antigen in either single or multiple specimens. The specimens used in this newly developed diagnostic technology can be tears, saliva, whole blood, serum, plasma, urine, stool, and other body discharges of animals or humans. In the food industry, the extracts of foods containing microorganisms or their toxins may be utilized.

2. Material and Methods

2.1. Solid Phase

The solid phase is a support material that supports active “sites” where antigens or antibodies are coated. The solid phase by itself can be the active sites of the device. In other words, the solid phase can be something similar to a credit card or the chips mounted on a credit card. The active parts of the device can be activated charcoal, plastic, gold, nitrocellulose membrane, latex, silicon or similar material. The antigens or antibodies should be immobilized on the active parts of the device. Coating can be on single or on multiple spots of the device. On a single solid phase, antigens or antibodies can be immobilized in a single spot of the active sites. For example, devices have the ability to detect specific IgE antibodies against a single allergen. To detect specific IgE antibodies to multiple allergens in a specimen in one run, many allergens can be coated at different spots of the solid phases’ active sites.

To show the feasibility in the study presented in this article, activated slides coated with CodeLink® HD, Surmodics, Inc., Eden Prairie, MN were mostly used as active sites.

In this study, for confirmation of the performance of the prototype detector and to demonstrate feasibility of the device, the data were obtained from a 200 μm field of the active sites. This means that in an active site area as big as 12 centimeter, at least 20 - 30 analytes could be coated. Example: 4 different antibodies to 4 major pathogens in a single food sample. The detection fields can be altered to higher or lower than 200 μm.

1Patent pending.
2.2. Principle and Procedure of the Method (Device)

The principle of the method presented in this study correlates directly with the inherent nature of proteins. Different proteins have varied and specific physical and chemical properties (charges), folding, stability, activity, and ultimately, specific functions. Antigens, antibodies, enzymes, allergens are all proteins or feature proteins as their main constituents. Each protein has its own net positive or net negative charges which are mainly related to their active or binding sites. They also have specific sizes (MW), shapes and configurations. The size of a protein (example: an antigen) is smaller in comparison to the same protein that is also bond to another protein (example an antibody) or vice versa. Likewise, the size of a protein/antibody complex is smaller than the size of a bound antigen/antibody/second antibody complex. Since proteins absorb UV light at 280 nm, larger sized proteins absorb more UV light (Example: antigen/antibody complex absorb more than an antigen alone). These fundamental properties for proteins were utilized in the development of the device presented in this study. Depending on the ultimate aims and design of the device, antibodies can be monoclonal or polyclonal.

The procedures and methods associated with the device include purified specific antigen or antibodies immobilized or coated on the active sites of the solid phase. After a reasonable incubation time, the non-specific binding sites on the solid phase were blocked by a solution containing a protein that did not interfere with the assay. After the blockage step, excess and unbound blocker was removed by washing and then slides were dried. This initial procedure should be done at manufacturing facilities and can easily be tailored towards the anticipated aims of device use.

On site, in diverse settings including laboratories, emergency rooms, ambulances, ambulatory physician offices, the end user operator(s) first read(s) the data (numerical or curve) by the detector at different spots of the device’s sites where specific antigens or antibodies are coated. Reading the data on the device depends on the design of the detector and should take approximately 1 minute. The numerical data obtained after the first reading is used as the base absorptions values (UV.D.). The specimen is then added at different parts of the active sites, where diverse antigens or antibodies are fixed. The specific antibodies against specific coated antigens (or vice versa) bind to the corresponding analytes. After a short incubation, excess specimen is washed by a specific wash solution. After drying, the data (numerical or curved) is read by the detector and absorbed UV.D.s. are compared with the baseline absorption readings obtained before addition of the specimen. Only parts of the active sites on the solid phase, on which specific antibodies (or antigens) from the specimen are bound, exhibit a different molecular size and therefore an augmented absorption. The increase in absorption depends on the levels (titer) of the specific antibodies (or antigens) in the specimen. The highest concentrations of the specific antibodies (or antigens) present in the specimen directly correlate with the lowest readings. In other words, elevated antibodies (or antigens) in the specimen translate to increased absorption and therefore lower numbers. The entire time to perform single or
multiple assays using the aforementioned technique is less than five minutes.

Using the device produces rapid, semi-quantitative data that can be used on-site for screening proposes.

If the application of the device is for detection of antibodies in multiple specimens against a single antigen (or vice versa) or if the aim is measuring the specific immunoglobulin (example: IgG) against an antigen, the device should be modified to prevent cross contamination. In this scenario, in order to measure the titer of a specific antibody to a specific antigen, the antigen/antibody complex is used as the baseline data and after addition of the second antibody to the device (example: Goat-anti-human IgG) and washing, the titer of IgG is measured numerically. Using the device for the purposes presented here is more complex and should be done in a laboratory setting by skilled personnel.

For any assay, the procedure should be optimized with cutoffs established.

2.3. Reader/Detector

Although promising data was obtained by using a Raman spectroscopy at 532 nm and UV micro spectroscopy, due to limitations including the size of the readers (not suitable for on-site testing) and a small detection field feasible for Raman spectroscopy (2 μm) and UV micro spectroscopy (100 μm), these readers were not used (patent pending).

In this study, a reader designed at Micro Detect, Inc. using Laser UV lights as the light source was operated. The designed UV system consists of a fiber optic multi-channel detection system that monitors and tracks changes in the optical transmission or reflection through a medium when utilizing a frequency modulated UV LED and a high sensitivity UV detector. This system uses a narrow bandwidth, high optical power, UV LED with peak emission intensity centered at 280 nm and a high sensitivity photodetector equipped with a band pass optical filter centered at 280nm and a pass bandwidth of ± 30 nm from the center wavelength. The Laser UV reader system can be integrated into an instrument (such as a small instrument similar to a credit card reader) to monitor the light intensity activity of the UV after absorption of UV by biomolecules (proteins) immobilized on the surface of a solid phase. The reader can be designed in a manner allowing the detection site of the reader (heads) to directly transfer the data to a previously programmed cellular phone or electronic tablet.

As proteins absorb UV light (around 280 nm), this device is mainly designed for the detection of proteins (most antigens and all antibodies are proteins). If the purpose of using this instrument is for detection of RNA or DNA, the wavelength can be changed to 260 nm.

The prototype instrument designed at Micro Detect, Inc. can be used for transmission (Figure 1) or reflection (Figure 2).

2.4. Specimens

The specimens used in this study were sera, stools, urines, extract of bacteria, or urine or stool spiked by desired analytes.
Figure 1. Transmission mode.

Figure 2. Reflection mode.
3. Results

Results from a number of studies are shown in the following Tables 1-10. The details associated with each study are presented corresponding to each study.

3.1. Precision

The *intra* and *inter* assay precisions was calculated by measuring UV.D. at 100 points (Replicates) on a slide coated with only *C. albicans* antigen (*Table 11*) and 100 points of coated slide plus a low positive serum for *C. albicans* antibodies using two independent operators (*Table 12*).

**Table 1.** The data related to several typical experiments performed to detect IgG antibodies to *H. pylori* antigen in human sera.

<table>
<thead>
<tr>
<th>Solid phase</th>
<th>CTR</th>
<th>CTTr</th>
<th>DTR</th>
<th>CTTr</th>
<th>NcR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blank</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.52*</td>
</tr>
<tr>
<td>Ag</td>
<td>0.42</td>
<td>0.42</td>
<td>0.42</td>
<td>0.53</td>
<td>0.51*</td>
</tr>
<tr>
<td>Ag + Pos1</td>
<td>0.39</td>
<td>0.31</td>
<td>0.39</td>
<td>0.35</td>
<td>0.47*</td>
</tr>
<tr>
<td>Ag + Neg 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.49*</td>
</tr>
<tr>
<td>Ag + Pos + Ab</td>
<td>0.36</td>
<td>0.11</td>
<td>0.37</td>
<td>0.32</td>
<td></td>
</tr>
</tbody>
</table>

C = Clear tap as solid phase, T = Tape, R = Reflection, Tr = Transmission, D = Dark tap as solid phase, Nc = Nitrocellulose membrane as solid phase, *Washing step was omitted.

**Table 2.** The data related to several typical experiments performed to detect IgG antibody to *H. pylori* antigen in human sera. The solid phase used to generate the data presented in this table is a glass slide coated with hydrophilic polymer containing epoxy reactive groups for immobilizing proteins.

<table>
<thead>
<tr>
<th>Solid phase</th>
<th>Exp Tr</th>
<th>Exp Tr</th>
<th>Exp Tr</th>
<th>Exp Tr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ag</td>
<td>0.47</td>
<td>0.47</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>Ag + Pos.</td>
<td>0.18</td>
<td>0.19</td>
<td>0.11</td>
<td>0.13</td>
</tr>
<tr>
<td>Ag + ½ pos.</td>
<td>0.33</td>
<td>0.25</td>
<td>0.31</td>
<td>0.20</td>
</tr>
<tr>
<td>Ag + ¼ Pos.</td>
<td>0.38</td>
<td>0.33</td>
<td>0.40</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Ep = Epoxy groups, Tr = Transmission, Exp. = Experiment.

**Table 3.** The data related to several typical experiments performed to detect IgG antibody to *C. albicans* antigen in a human serum. The solid phase used to generate the data presented in this table is a glass slide coated with hydrophilic polymer containing epoxy reactive groups for immobilizing proteins.

<table>
<thead>
<tr>
<th>Solid phase</th>
<th>Exp Tr</th>
<th>Exp Tr</th>
<th>Exp Tr</th>
<th>Exp Tr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ag</td>
<td>0.49</td>
<td>0.49</td>
<td>0.44</td>
<td>0.44</td>
</tr>
<tr>
<td>Ag + Pos.</td>
<td>0.12</td>
<td>0.11</td>
<td>0.12</td>
<td>0.11</td>
</tr>
<tr>
<td>Ag + ½ pos.</td>
<td>0.34</td>
<td>0.26</td>
<td>0.19</td>
<td>0.20</td>
</tr>
<tr>
<td>Ag + ¼ Pos.</td>
<td>0.43</td>
<td>0.37</td>
<td>0.26</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Ep = Epoxy groups, Tr = Transmission, Exp. = Experiment.
Table 4. High density amine-binding groups slide, transmission mode for detection of antibodies against *Helicobacter pylori* antigen.

<table>
<thead>
<tr>
<th>UV.D.</th>
<th>ELISA (ODs)</th>
<th>Sera</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ag alone</td>
<td>IgA*</td>
</tr>
<tr>
<td></td>
<td>Ag plus samples</td>
<td></td>
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<tr>
<td>IgG+</td>
<td>0.49</td>
<td>0.560</td>
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<tr>
<td>IgG+</td>
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<td>0.39</td>
</tr>
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<td>IgG+</td>
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<td>IgG+</td>
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<td>0.47</td>
</tr>
<tr>
<td>IgG+</td>
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<td>0.46</td>
</tr>
<tr>
<td>IgG−</td>
<td>0.49</td>
<td>0.43</td>
</tr>
<tr>
<td>IgG−</td>
<td>0.49</td>
<td>0.46</td>
</tr>
<tr>
<td>IgG−</td>
<td>0.49</td>
<td>0.44</td>
</tr>
<tr>
<td>IgG−</td>
<td>0.49</td>
<td>0.45</td>
</tr>
</tbody>
</table>

*Tested on FDA cleared products. N/D: not done.

Table 5. High density amine-binding groups slide, transmission mode, detecting antibodies to Ds-DNA.

<table>
<thead>
<tr>
<th>UV.D.</th>
<th>ELISA* IgG</th>
<th>Specimens</th>
<th>Sera</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ag** alone</td>
<td>Ag plus samples</td>
<td></td>
</tr>
<tr>
<td>IgG+</td>
<td>0.50</td>
<td>0.33</td>
<td>+</td>
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<td>IgG+</td>
<td>0.48</td>
<td>0.30</td>
<td>+</td>
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<tr>
<td>IgG+</td>
<td>0.50</td>
<td>0.34</td>
<td>+</td>
</tr>
<tr>
<td>IgG+</td>
<td>0.48</td>
<td>0.26</td>
<td>+</td>
</tr>
<tr>
<td>IgG+</td>
<td>0.50</td>
<td>0.43</td>
<td>+</td>
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<tr>
<td>IgG+</td>
<td>0.50</td>
<td>0.53</td>
<td>−</td>
</tr>
<tr>
<td>IgG+</td>
<td>0.50</td>
<td>0.50</td>
<td>−</td>
</tr>
<tr>
<td>IgG−</td>
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<td>−</td>
</tr>
<tr>
<td>IgG−</td>
<td>0.48</td>
<td>0.51</td>
<td>−</td>
</tr>
<tr>
<td>IgG−</td>
<td>0.48</td>
<td>0.50</td>
<td>−</td>
</tr>
</tbody>
</table>

*Tested on a FDA cleared product. **Ag is not a protein.

Table 6. High density amine-binding groups slide, transmission mode, pregnancy test for detection of hCG hormone.

<table>
<thead>
<tr>
<th>UV. D.</th>
<th>Lateral flow</th>
<th>Urine specimens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ab* alone</td>
<td>Ab Plus samples (Ags)</td>
</tr>
<tr>
<td></td>
<td>0.39</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>0.39</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>0.39</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>0.39</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>0.39</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>0.37</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>0.38</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>0.38</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>0.39</td>
<td>0.38</td>
</tr>
</tbody>
</table>

*Anti-hCG.
Table 7. High density amine-binding groups slide, transmission mode, detecting antibodies to latex (Allergen).

<table>
<thead>
<tr>
<th>Sera</th>
<th>UV.D.</th>
<th>Clinical results</th>
<th>ELISA ODs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ag** alone</td>
<td>Ag plus samples (Abs)</td>
<td>Skin test</td>
</tr>
<tr>
<td>1</td>
<td>0.55</td>
<td>0.43</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>0.55</td>
<td>0.41</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>0.55</td>
<td>0.45</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>0.55</td>
<td>0.37</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>0.55</td>
<td>0.44</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>0.55</td>
<td>0.52</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>0.55</td>
<td>0.51</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>0.55</td>
<td>0.50</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>0.55</td>
<td>0.51</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>0.50</td>
<td>0.53</td>
<td>–</td>
</tr>
</tbody>
</table>

**Ag is latex protein.

Table 8. Detection of *H. pylori* antigen in stool test, transmission mode.

<table>
<thead>
<tr>
<th>Ab* alone</th>
<th>Ab Plus samples (Ags)</th>
<th>Lateral flow, stool test</th>
<th>Serum IgG ELISA</th>
<th>Stool Specimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.43</td>
<td>0.25</td>
<td>+</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>0.43</td>
<td>0.23</td>
<td>+</td>
<td>N/A</td>
<td>Spiked negative</td>
</tr>
<tr>
<td>0.43</td>
<td>0.29</td>
<td>+</td>
<td>Positive</td>
<td>3</td>
</tr>
<tr>
<td>0.45</td>
<td>0.24</td>
<td>+</td>
<td>Positive</td>
<td>3 repeat</td>
</tr>
<tr>
<td>0.43</td>
<td>0.28</td>
<td>+</td>
<td>weak Pos.</td>
<td>+/-</td>
</tr>
<tr>
<td>0.43</td>
<td>0.43</td>
<td>–</td>
<td>Negative</td>
<td>N/D</td>
</tr>
<tr>
<td>0.40</td>
<td>0.40</td>
<td>–</td>
<td>Negative</td>
<td>N/D</td>
</tr>
<tr>
<td>0.43</td>
<td>0.40</td>
<td>–</td>
<td>Negative</td>
<td>N/D</td>
</tr>
<tr>
<td>0.43</td>
<td>0.40</td>
<td>–</td>
<td>Negative</td>
<td>4</td>
</tr>
<tr>
<td>0.43</td>
<td>0.43</td>
<td>–</td>
<td>Negative</td>
<td>3 repeat***</td>
</tr>
<tr>
<td>0.43</td>
<td>0.42</td>
<td>–</td>
<td>Negative</td>
<td>1 repeat ***</td>
</tr>
</tbody>
</table>

*Anti-*H. pylori. **Treated for *H. pylori* infection 2 months before performing the test. ***Samples were taken immediately after treatment.


<table>
<thead>
<tr>
<th>Ab* alone</th>
<th>Ab Plus samples (Ags)</th>
<th>Lateral flow</th>
<th>Specimens Strep. A. samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.46</td>
<td>0.29</td>
<td>+</td>
<td>Positive Control**</td>
</tr>
<tr>
<td>0.46</td>
<td>0.32</td>
<td>+</td>
<td>Positive (2)</td>
</tr>
<tr>
<td>0.45</td>
<td>0.35</td>
<td>+</td>
<td>1/2 2</td>
</tr>
<tr>
<td>0.45</td>
<td>0.37</td>
<td>+</td>
<td>1/4 2</td>
</tr>
<tr>
<td>0.46</td>
<td>0.40</td>
<td>+</td>
<td>1/8 2</td>
</tr>
<tr>
<td>0.44</td>
<td>0.42</td>
<td>–</td>
<td>Negative Control**</td>
</tr>
<tr>
<td>0.44</td>
<td>0.42</td>
<td>–</td>
<td>Swab taken from a healthy subject</td>
</tr>
<tr>
<td>0.44</td>
<td>0.42</td>
<td>–</td>
<td>Swab taken from a healthy subject</td>
</tr>
</tbody>
</table>

*Anti-*Strep. A. **From approved device.
Table 10. Transmission mode, multiple analytes tests. Detecting antigens and/or antibodies in one run in one spiked specimen.

<table>
<thead>
<tr>
<th>Coated on the slide</th>
<th>UV. D.</th>
<th>Methods used for confirmation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base UV.D.</td>
<td>UV. D. after adding the specimen</td>
</tr>
<tr>
<td>Anti-\textit{H. pylori} Ab</td>
<td>0.27</td>
<td>0.18</td>
</tr>
<tr>
<td>Anti-\textit{Strep. A} Ab</td>
<td>0.25</td>
<td>0.13</td>
</tr>
<tr>
<td>Anti-hCG</td>
<td>0.27</td>
<td>0.11</td>
</tr>
<tr>
<td>Latex antigen</td>
<td>0.22</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Blank = 41. Specimen = Equal volume of a urine specimen positive for hCG (50%) and a serum positive for IgE to latex (allergen) (50%). Artificial preparation. This mixture was spiked with strep A. antigen and \textit{H. pylori} antigen.

Table 11. Precision of a typical experiment. Slide is coated only with Ag.

<table>
<thead>
<tr>
<th></th>
<th>Intra</th>
<th>Inter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Operator 1</td>
<td>Operator 2</td>
</tr>
<tr>
<td>Average</td>
<td>0.514653</td>
<td>0.5126</td>
</tr>
<tr>
<td>STDEV</td>
<td>0.009845</td>
<td>0.009494</td>
</tr>
<tr>
<td>%CV</td>
<td>1.91299</td>
<td>1.852182</td>
</tr>
<tr>
<td>Number</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 12. Precision of a typical experiment. Slide is coated with Ag. plus a weak positive specimens (low Ab).

<table>
<thead>
<tr>
<th></th>
<th>Intra</th>
<th>Inter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Operator 1</td>
<td>Operator 2</td>
</tr>
<tr>
<td>Average</td>
<td>0.47396</td>
<td>0.4711</td>
</tr>
<tr>
<td>STDEV</td>
<td>0.01116</td>
<td>0.009629</td>
</tr>
<tr>
<td>%CV</td>
<td>2.354721</td>
<td>2.043935</td>
</tr>
<tr>
<td>Number</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

3.2. Linearity
The UV.D. values for two preparations tested independently were obtained using two-fold serial dilutions of each preparation. The protein used for preparations was BSA. The UV.D. values at 280 nm were compared to log2 of dilution by standard linear regression. The resulting data are in Figure 3.

3.3. Performance
The assay results using 92 confirmed \textit{H. pylori} positive and negative specimens were compared with the results obtained for the same specimens when tested on two FDA cleared predicate kits (IgG and IgA).

Correlation study was conducted on all 92 patients’ sera. Of the 92 patients specimens used in this study 80 were negative and 12 were positive for the pre-
The performance, when using UVLSD device for detection of antibodies to *H. pylori* on tested sera gave the following results:

Sensitivity = \( \frac{TP}{TP + FN} \times 100 = \frac{12}{12 + 0} \times 100 = 100\% \)

Specificity = \( \frac{TN}{TN + FP} \times 100 = \frac{80}{80 + 3} \times 100 = 96\% \)

Efficiency = \( \frac{(TP + TN)}{(TP + TN + FP + FN)} \times 100 = \frac{(12 + 80)}{(12 + 80 + 3 + 0)} \times 100 = 96.8\% \)

Positive predictive value = \( \frac{TP}{TP + FP} \times 100 = \frac{12}{12 + 3} \times 100 = 80\% \)

Negative predictive value = \( \frac{TN}{TN + FN} \times 100 = \frac{80}{80 + 0} \times 100 = 100\% \)

4. Conclusions and Applications

The UV Laser Spectroscopy Diagnostic method (device) used in this study demonstrated very good performance, as indicated by accepted linearity and low inter and intra CV values.

Results obtained by testing different type of specimens, (urine, serum, stool or extract of bacteria) show that the device can be used for the detection of antibodies to *Helicobacter pylori* (Bacteria), *Candida albicans* (yeast), Ds-DNA (autoimmune marker) and Latex (allergen). Likewise, results show that the device can be used for the detection of antigens of *H. pylori* in stool, Strep. A. in a spiked solution, and hCG (hormone) in urine. Generated results associated with each analyte directly correspond with the results obtained by using predicate devices and methods.

Results demonstrate that in one assay’s run, antibodies to a single target antigen (Tables 3-6) or an antigen to a single target antibody can successfully be performed. The device demonstrates accepted data for the detection of IgE antibody to latex allergen and antibody to Ds-DNA.

One important aspect of using the device is its application for detection of multiple antigens, antibodies, or a mixture of antigen/antibody in a single spe-
cimen to multiple analytes. Table 10 shows that in one assay’s run, simultaneous antigens of Sterp. A. and antigen of \( H. pylori \) were detected by anti-Strep. A. antibody and anti-\( H. pylori \) antibody respectively. Table 10 also demonstrates detecting hCG (a hormone) in the same spiked specimen. In the same assay, the latex allergen was used to detect IgE antibody to latex. For evaluation of the device amongst a vast combination of analytes, the specimens used for data generation presented in Table 10 were artificially spiked with the desired analytes.

Our study assessed the clinical utility of the device by using 92 clinically confirmed specimens (Table 13). In this well-controlled study, 12 positive and 80 negative were tested with the predicate FDA cleared kits. The same samples were tested for antibodies to \( H. pylori \) on the UVLSD device. Data presented in Table 13 manifests the acceptable sensitivity and specificity.

With appropriate modification, the device can be used for the detection of antigens or antibodies in several specimens simultaneously. In this study, we did not use the device for this purpose as for cross-contamination prevention we had to modify the solid phase. This application of the device is particularly useful in the blood bank (for example when detection of antibodies to hepatitis B antigen in many specimens is the aim of running the assay in a short time.) Using the device in this format not only is applicable for screening proposes, but can also be used for detection of specific antibodies e.g. IgG, IgM, IgA or IgE.

The total time for running an assay by the end users is less than 5 minutes. Since a vast combination of assays using desired analytes can be tested on this device and single or multiple results can be obtained in a relatively short time, the device can be considered as an easy to use device for on-site or point of care screening purposes.

The data obtained by testing stools specimens (Table 8) demonstrate that the device can be used for longitudinal follow up of treatment as well. Specimen # 2 was treated for \( H. pylori \) infections two months before testing the stool on the device. Also, sample 1 and 3 were tested on the device before and a few days after completion of the treatments.

Another useful opportunity for this device is the discipline of forensic medicine. Since the absorbed antigens or antibodies on the solid phase are proteins, if the device is properly maintained in an appropriate environment, the results of the test can be preserved for several years.

The following are select examples that demonstrate various applications of the device:

Table 13. Assay performance.

<table>
<thead>
<tr>
<th>Specimens</th>
<th>( H. pylori ) IgG or IgA or IgM or combination of them</th>
<th>UVLSD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>12</td>
<td>12 (TP)</td>
<td>0 (FN)</td>
</tr>
<tr>
<td>Negative</td>
<td>80</td>
<td>3 (FP)</td>
<td>77 (TN)</td>
</tr>
<tr>
<td>Total</td>
<td>92</td>
<td>15</td>
<td>77</td>
</tr>
</tbody>
</table>

*\( H. pylori \) ELISA assay results tested on approved predicate.
1) For major food allergies, a panel of allergens such as peanut, tree nuts, milk, egg, wheat, soy, fish and shellfish can be coated on different spots of the solid phase at the manufacturing facility. On site, the end users may use a single specimen (for example a drop of whole blood obtained from a finger prick) to screen for the presence of IgG (and IgE) antibodies to the above allergens in a rapid manner (food allergies are considered a delayed IgG mediated allergy).

2) Likewise, for other major allergies, a panel of allergens such as dog, penicillin, latex, selected pollens, cat, molds and house dust mite can be coated on different spots of the solid phase at the manufacturing facility. On site, the end users may use a single specimen (for example a drop of whole blood obtained from a finger prick) to screen for the presence of IgE antibodies to the above allergens in a short time. IgE mediated allergies are dangerous and may cause anaphylactic shock and sudden death.

3) One of the main utilities of the device is for emergency purposes. For example, to assess heart failure or a heart attack in rapid manner, a panel consisting of anti-CK, anti-Tn I, anti-Tn T, anti-CRP (not specific), anti-AST, anti-BNP, and anti-GPBB can be coated on different spots of the solid phase at the manufacturing facility. On site, the end users may use a single specimen (for example a drop of whole blood obtained from a finger prick) to determine presence of all or any number of cardiac injury markers which can then be associated with disease severity.

4) In the food industry, for determination of major food borne pathogens in a sample, a panel consisting of anti-Campylobacter jejuni, anti-E.coli O157:H7, anti-Shigella, anti-Salmonella, anti-Listeria, and anti-Norovirus can be coated on different spots of the solid phase at the manufacturing facility. On site, the end users may use a single sample (for example a drop of meat extract) to determine the presence of all or any one of the contaminants.

5) For determination of autoimmune disorders, a panel (ENA) consisting of SS-A, RNP, SS-B, Jo1, Scl-70 and Sm proteins can be coated on different spots of the solid phase at the manufacturing facility. On site, the end users may use a single specimen (for example a drop of whole blood obtained from a finger prick) and determine the presence of antibodies to all or any one of the coated proteins.

6) For rapid determination of the presence of drugs in urine in criminal cases or for controlled substance prescription and monitoring, a panel of major drugs consisting of antibodies to drugs such as: Marijuana, cocaine, opioid pain relievers, benzodiazepines, heroin, methamphetamine etc. can be coated on different spots of the solid phase at the manufacturing facility. On site, the end users may use a single specimen (mostly urine) and determine the presence of one or more of the coated antibodies.

7) The device can also be used for many other proposes such as testing the HIV P24 protein in blood in emergency room settings or for rapid determination of D-dimer in the operating room. Likewise, the device can be designed for panels utilized in GI pathology, STDs, pulmonology, etc.
Manufacturing any format of the device should be done following regulations, guidelines and appropriate quality and efficacy measures. The prepared devices should be optimized with the cutoff for each analyte properly established with data related to each analyte stored in the device detector or reader for on-site or point of care evaluation.

References


**Abbreviations**

Ab = Antibody
Ag = Antigen
AST = Aspartate Transaminase
BNP = B-type natriuretic peptide or Brain natriuretic peptide
BSA = Bovine Serum Albumin
CK = Creatinine Kinase
CRP = C-reactive protein
CV = Coefficient of Variation
DNA = Deoxyribonucleic Acid
Ds-DNA = Double stranded Deoxyribonucleic Acid
ELISA = Enzyme-Linked Immunosorbent Assay
ENA = Extractable Nuclear Antigens
FDA = Food and Drug Administration
FN = False Negative
FP = False Positive
GI = Gastrointestinal
GPBB = Glycogen Phosphorylase Isoenzyme BB
hCG = human Chorionic Gonadotropin
HIV = human immunodeficiency virus
HpAg = *Helicobacter pylori* antigen
IgA = Immunoglobulin A
IgE = Immunoglobulin E
IgG = Immunoglobulin G
IgM = Immunoglobulin M
Jo1 = Histidine-tRNA ligase (also called Jo-1)
LED = light-emitting diode
MW = Molecular Weight
N/A = Not Applicable
N/D = Not Done
O.D. = Optical Density
PCR = Polymerase Chain Reaction
RIA = Radioimmunoassay
RNA = Ribonucleic Acid,
RNP = Ribonucleoprotein
SS-A (Ro) = Sjogren’s Syndrome A
SS-B (La) = Sjogren’s Syndrome B
Scl-70 = Scleroderma 70 KD
Sm = Sm Ribonucleoproteins
STD = Sexually Transmitted Diseases
TN = True Negative
TP = True Positive
Tn I = Troponin I
Tn T = Troponin T
UV = Ultra Violet
UV. D. = Ultra Violet Density
UVLSD = UV Laser Spectroscopy Diagnostic
Improving Balance through Virtual Reality and Physical Therapy Integration

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Abstract

**Background and Purpose:** Virtual reality (VR) is an innovative technology that shows promise in the assistance of physical therapy (PT). This case report explores the use of virtual reality with a patient suffering from unilateral vestibular hypofunction (UVH). **Case Description:** The patient is a 50-year-old male who was referred to physical therapy following a motor vehicle accident. The patient was diagnosed with having an acute left UVH, accompanied by reports of dizziness, imbalance and gait disturbances which impaired him from his work in construction. **Intervention:** The patient was seen two to three times a week for 40-minute sessions along with an individualized home exercise program. Interventions included vestibular rehabilitation exercises, balance training, gait training, and VR. The goals of VR were to provide task-specific simulations to improve postural balance, decrease anxiety through exposure therapy, and improve smooth eye pursuits to improve static balance. **Outcomes:** Outcomes used included subjective questionnaires such as the Activities-Specific Balance Confidence survey and the Dizziness Handicap Inventory (DHI) as well as functional tests like the Sensory Organization Test, Motor Control Test, and the Functional Gait Assessment (FGA). Outcome measures were performed at initial evaluation, at the 10th visit, and again at discharge. Notable improvements were seen on DHI and FGA scores. **Conclusion:** Dizziness, confidence, balance, and gait improved following vestibular rehabilitation combined with VR. Outcomes of this case suggest that virtual reality in conjunction with vestibular rehabilitation therapy is effective in improving deficits of unilateral vestibular hypofunction. Additionally, the use of VR in this case report suggests this can be an effective tool for intervention to facilitate patient-specific goals.

**Keywords**

Physical Therapy, Acute Unilateral Vestibular Hypofunction, Virtual Reality, Vestibular Rehabilitation
1. Introduction

Modern technology and the advent of the internet have changed the structure and organization of the entire medical field. Technology has given the fragmented nature of healthcare more efficient ways to sort through the large volume of transactions within the system, a way to provide the need to integrate new scientific evidence into practice, organize other complex information management activities, and free the limitations of paper-based information management [1]. New systems and technologies have been implemented to ease the transfer of information from one person to another. From the widespread adoption of electronic medical records to advances in bio-medical engineering and technology, modern healthcare and its delivery methods are continually changing. Due to the continually expanding body of knowledge in health care, practitioners who rely on their memory and personal experience are obsolete [1]. Electronic medical records have increased the efficiency of clinical practice, reduced human errors, and increased the quality of care. The increased connectivity of the internet has given rise to telecommunication. Patients now have access to speak to any a medical professional through the simple press of a button. Practitioners are also able to create virtual conferences with other professionals across the globe. The age of information has continued to evolve into the technological revolution of the 21st century. Not only has technology allowed an improved way to share information, but it has brought forth inventions of improved diagnostic tools within health care. Some of these tools include radiographic images, angiograms, ultrasound, nerve conduction, electrocardiograms, and electroencephalograms, just to name a few. Technology is continuously growing and useful in everyday life. New technology has been integrated into healthcare and has created better access to medical records, exchange of data, visualization of the human body, and assistance with the evaluation and treatment of patients. A newer, revolutionary technology, virtual reality, has continued to show promise as a rehabilitative tool.

Virtual reality (VR) is defined as an artificial environment which is experienced through sensory stimuli provided by a computer and in which one’s actions partially determine what happens in the environment [2]. Previously, VR technology had a patient placed onto a screen in which the patient would see themselves as an avatar within a virtual world. Today, we are able to immerse people into a virtual world where their movements are tracked within a 3 dimensional plane where they are able to manipulate and maneuver within the virtual environment. Continuing advances in VR technology and system cost reductions have allowed this technology to be accessible to the masses. Most VR systems primarily deliver visual and auditory feedback [3]. Information is displayed by head-mounted displays, projections systems, or a flat screen of varying sizes. Special applications and accessories may be necessary to run with these display systems [3] [4]. VR allows for control, customization and freedom within a given environment.

The first health care applications of VR started in the early 90s by the need of
medical staff to visualize complex medical data, particularly during surgery and for surgery planning. At this time, the surgery-related applications of VR fell under these categories: surgery training, surgery planning and augmented reality for surgery sessions in open surgery, endoscopy, and radiosurgery [5]. In the following years, VR applications were developed and broadened to include neuropsychological assessment and rehabilitation. Even with the ability of variance and customization of VR, the gap between the virtual experience and the complexity of real life was far too much.

With our advances in technology, VR has become the forefront and is considered one of the most innovative technologies and promises to have a considerable impact on rehabilitation [3]. New VR systems and applications have the ability to uniquely target a broad range of physical, psychological, and cognitive rehabilitation concerns [4]. Each application requires special software development tools to design an interactive simulated environment that can help achieve patient-therapist centered goals. With open-source applications readily available online, enormous quantities of information can be shared and utilized with the needs of various rehab professionals. Bermudez i Badia et al. are developing the Open Rehab Initiative that gives rehabilitation professionals a quick and easy way to access virtual programs for rehabilitation. It is an independent online portal that aims to help clinicians, scientists, engineers, game developers and end-users to interact with and share virtual rehabilitation tools. Along with the open-access of newly developed software, newer and more cost-effective VR headsets are being released. Integration of mobile devices along with some headsets have allowed for a cheaper alternative to the VR experience.

Some VR applications are being used to assist with assessment and treatment as a tool in rehabilitation [3] [4] [6]. To date, most VR systems primarily deliver visual and auditory feedback. Applications that are available allow individuals to experience a multitude of virtual environments and access to virtual avatars. These environments may simulate life situations that may include a virtual kitchen, a shopping isle, street crossing, tightrope walking, and virtual theme parks. Newer programs are being created that allow a person to manipulate virtual objects within a virtual world. Clinical psychologists and rehabilitation specialists use VR to provide new human-computer interactions [4]. This allows participants to engage in active participation within a computer-generated three-dimensional world rather than passive observers. Early research agrees that VR can assist with the facilitation of therapeutic change [3] [4]. This case report will follow closely with the integration of VR along with rehabilitation therapy in an outpatient vestibular physical therapy setting.

Those suffering from vestibular deficits commonly have complaints in the form of “dizziness”. Some forms of dizziness include light-headedness or faintness, nausea, unsteadiness of one’s feet, or vertigo. These symptoms can be caused by lesions anywhere in the vestibular pathway. Most cases are caused by peripheral disorders involving the inner ear, with central disorders of the brainstem or cerebellum being less common [7]. Those receiving treatment for
these symptoms perform vestibular rehabilitation. Vestibular rehabilitation is an exercise-based treatment program designed to promote vestibular adaptation and substitution. Key exercises for vestibular rehabilitation are head-eye movements, maintaining balance with various orientations of head and trunk, repeating movements that provoke vertigo-like symptoms, and gradually exposing patients to various sensory and motor environments. The main goals for vestibular rehabilitation are to enhance gaze stability, enhance postural stability, improve vertigo, and to improve activities of daily living [8].

Increasing availability of VR technology and the creation of more interactive VR applications have helped integrate VR into today’s society. VR technology provides a level of customization, control, and adaptability to virtual environments. VR offers the ability to create systematic human testing, training, and treatment environments. The variability of VR allows for sophisticated interactions, behavioral tracking, and performance recording. Similarly to vestibular rehabilitation, VR applications have the potential mimic movements and positions seen within the key exercises of vestibular rehabilitation.

A study by Kim et al. explores the link between smooth eye pursuits without head movement and its disruption to static balance [9]. Results of the study show a positive correlation with eye movements and disturbance of static equilibrium. This study implies the importance of gaze stability and oculomotor control in those suffering from balance deficits. In physical therapy, patients with central nervous system injuries may present with impairments with eye movements. Virtual environments can be used as a tool to assist in oculomotor exercises [9]. To objectively measure the amount of adaptation and habituation, the Dizziness Handicap Inventory (DHI), with minimal detectable change (MCD) of 18, was used to quantify the patient’s self-perception [10]. DHI has is valid and has high test-retest reliability for total score \( r = 0.97, \, df = 12, \, p < 0.0001 \), for sub-scale scores \( r = 0.92 - 0.97, \, p < 0.001 \) [11].

A study by McConville and Milosevic, suggests that active video games could be used to improve postural balance by challenging the vestibular system with various head movements [12] [13]. Some applications available include active video games that place a person into head positions that are seen in a vestibular rehabilitation program. Another study by Meldrum et al. tests the effectiveness of VR-based vestibular rehab compared to conventional rehab [14]. The results show that VR is a portable tool patients can take home and that therapists can use to record adherence and compliance to the program. To measure objective changes in balance, the Sensory Organization Test (SOT) was used. This outcome measure has an MDC of 8 points [15]. The SOT has adequate composite score reliability \( (ICC = 0.67) \) and has moderately high sensitivity (85%) and specificity (77%) in identifying vestibulopathies [15].

A randomized controlled trial by Kalron et al., examined the efficacy of a 6-week VR balance training program for those with multiple sclerosis using the computer assisted rehabilitation environment (CAREN) system [16]. Results imply that the balance training based on the CAREN device is an effective me-
Method of balance training for those with imbalance. The CAREN system shows that VR is capable of improving a patient’s balance [16]. To measure improvements within functional balance, the Functional Gait Assessment (FGA) was performed. This measure has a MDC of 8 points [17]. The FGA has excellent test-retest reliability when administered by a student (ICC = 0.80; 95% CI = 0.58 - 0.91), excellent interrater reliability (ICC = 0.84), and excellent internal consistency (α = 0.79) [18].

A study by Maron et al. explores the physiological and behavioral indicators of anxiety during exposure in a VR environment [19]. In the study, participants who had acrophobia were immersed into a virtual cityscape at varying heights. Baseline measurements were recorded without VR, in VR at ground level, and in VR at height. The results showed that patients demonstrated the physiological and behavioral indicators when immersed in a virtual environment. A case study by Whitney et al. explores VR exposure therapy together with physical therapy to assist in the improvement of Acrophobia and pathological height vertigo [20]. These studies show a positive correlation between VR exposure therapy and decreased anxiety levels due to acrophobia. The virtual environment is so complex that it can trick the brain into perceiving a virtual object as real, triggering a physiological response. To get an objective measurement of this, the Activities-Specific Balance and Confidence Scale (ABCs) was used. This measure has a MDC of 12 [21]. The ABC has excellent test-retest reliability (r = 9.2, p < 0.001), excellent internal consistency (α = 0.96) [22] [23].

As current technologies continue to advance as well as continued research on VR, we will be one step closer to fully integrating virtual worlds into our everyday experiences. Current research has shown promise in the use of virtual environments and their effectiveness in the health care industry. As more low-cost hardware becomes readily available, it will be easier for VR to assimilate with society [3] [4]. Physical therapists can look forward to seeing VR as an assistive tool that will help provide a more efficient way to provide our patients the best treatment. The purpose of this case is to view the effectiveness of VR combined with traditional vestibular rehabilitation with a patient who poor postural control and a diagnosis of vestibular hypofunction.

2. Case Description

AR is a 50-year-old male who presents to the clinic with a referral from his physician stating imbalance and dizziness following a motor vehicle accident (MVA) 6 weeks ago. The patient complained of blurry vision, ringing in the ears, and difficulty remembering things. He reports that symptoms increase with quick head movements and eases with rest. The patient has a history of asthma that is controlled. The patient has an endomorph body type and has not been very active outside of work. The patient works for a construction company which requires him to travel on-site and perform duties in high, elevated areas. He has a supportive family and likes to go out and spend time with his significant other and his daughter. The patient completed and signed an informed consent and
An examination was performed that includes the patient history, a systems review, and test and measures to gather patient data as described in The Guide to Physical Therapy Practice [24]. The patient completed objective measures the Dizziness Handicap Scale (DHI) Activities-Specific Balance Confidence Scale (ABCs), Functional Gait Assessment (FGA), Sensory Organization Test (SOT), and Motor Control Test (MCT). The DHI and ABCs are surveys that were designed to objectively measure the patient’s subjective history of their ongoing impairments. The patient scored a 74 on the DHI which places him in the category of severe vestibular dysfunction [25]. With the ABCs, he scored a 75% which places him within normative values at his age range [22]. Upon gathering history, the patient described his dizziness as a swaying sensation as if he was “riding a boat.” He stated a feeling of disequilibrium and dizziness lasting between 10 seconds to 30 seconds. Ease of symptoms occurred with rest and with his eyes closed. The patient reported not taking any medications. During the physical examination, the patient presented with a presence of saccadic eye movements during smooth-purist movements and complained of an increase in dizziness symptoms. The patient demonstrated a loss of vergence of the left (L) eye at 15 cm. A Head Impulse Test (HIT) was performed and the patient demonstrated a positive HIT on his L side. The patient performed full cervical range of motion (ROM) without pain. His lower extremity strength was within normal limits. Functional tests, FGA, SOT, and MCT, were used to give the physical therapist a better understanding how the patient moves within certain conditions. The patient scored a 21/30 with the FGA which places him below the normative values at his age [26]. A NeuroCom SMART Balance Master® device was available to assist in performing the SOT and MCT. SOT revealed a vestibular dysfunction and gave a composite score of 67 which placed him below the normative values at his age [27]. For MCT, the patient received a composite score of 142 which places him within normal values at his age [27]. Reflexes and sensation were normal and intact. No radiographic images were provided.

3. Patient Evaluation

The patient presents with a composite impairment of decreased balance. Indirect impairments include increased dizziness, blurry vision, and tinnitus. Secondary impairments include disequilibrium and gait disturbances. With the given information, it is suspected that the patient has a diagnosis of unilateral L sided vestibular hypofunction. Since the patient explained an increase of symptoms with quick head movements, a differential diagnosis of benign paroxysmal positional vertigo (BPPV) was explored. The patient demonstrated a pain-free cervical range of motion (ROM). The patient’s description of symptoms is not consistent with symptom presentation of BPPV and did not present with nystagmus during the Dix Hallpike. A positive HIT suggests the presence of a unilateral peripheral vestibular weakness on the L side [28]. The DHI also supports this hypothesis and places the patient in the category of severe vestibular dysfunction.
Scores from SOT further support of a vestibular deficit. The ABCs and MCT reveal that the patient is a decreased risk of sustaining a fall. Values of FGA, broken up in Table 1, suggest that the patient with a mild balance impairment. The patient demonstrated noted difficulties with gait with horizontal head turns, gait with a narrow base of support, gait with eyes closed and backward ambulation.

According to the International Classification of Functioning, Disability, and Health (ICF) [29], the patient activity limitations include ambulation and reading for longer than 30 minutes. Participation limitations include the inability to perform job requirements, driving long distances, enjoying theme parks with his family. Based on these limitations, the patient received a physical therapy diagnosis of R26.81 Unsteadiness on feet and R42 Dizziness and Giddiness.

4. Plan of Care

Following the physical therapy examination and evaluation, a plan of care was discussed with the patient and short- and long-term goals were established. The patient agreed to being seen two to three times a week for eight weeks with 40-minute sessions at an outpatient vestibular setting [30] [31]. Short-term goals were to be accomplished in the four weeks which included: decreasing DHI score to 50 on DHI and increasing ABCs score to 82%. The primary focus within the first four weeks was to improve his acute unilateral vestibular hypofunction and to prepare him for more complex challenges with VR [31]. Clinical practice guidelines recommend that patients with acute unilateral vestibular hypofunction should have supervised therapy for two to three weeks [31]. Research has shown that patients suffering from vestibular deficits may require up to 8 weeks of vestibular therapy before seeing significant improvement [30]. Long-term goals expected to be accomplished by discharge, included: an increase in ABCs scores to >92%, improvement of FGA score > 26, improved SOT composite score > 75, and a negative HIT.

Table 1. FGA scores.

<table>
<thead>
<tr>
<th></th>
<th>T1</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gait on Level Surface</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Change in Gait Speed</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Gait with Horizontal Head Turns</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Gait with Vertical Head Turns</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Gait and Pivot Turn</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Step over Obstacle</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Gait with Narrow Base of Support</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Gait with Eyes Closed</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Ambulating Backwards</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Steps</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total Score</strong></td>
<td><strong>21</strong></td>
<td><strong>29</strong></td>
</tr>
</tbody>
</table>

T1—Initial evaluation, T3—Discharge.
The patient’s prognosis was good to achieve both short and long-term goals as he demonstrated high levels of motivation, a supportive family, and a minimally active lifestyle. Early treatment strategies included vestibular exercises, balance training, and gait training [9] [31] [32]. At follow-up, the patient was introduced to a VR environment. VR has shown promise with the psychological as well as physical aspects of rehabilitation [4] [14] [19]. The purpose for VR was to challenge his balance systems further and incorporate new strategies to enable him to return to full-time work status.

5. Implementation of Interventions/Re-Assessment

Interventions utilized during the patient’s therapy focused on improving vestibular function to improve overall balance [9] [32]. The patient was cleared of any cervical restrictions that may impede vestibular exercises. The patient had no complaints of neck pain, focal neck tenderness or spasms, or any neurological deficits. The patient was educated on the importance of maintaining a consistent exercises program and that he would see significant changes in his overall balance for approximately 8 weeks [30]. With exercises and activities, the patient was placed into a harness which was attached to a ceiling track to prevent a fall. A supervised student physical therapist was present to assist the patient if he were to experience a loss of balance.

During the first four weeks, the patient engaged in vestibular rehabilitation therapy [8] [31]. Exercises performed were to improve gaze stability, enhance eye movements, increase postural stability, decrease vertigo, and improve activities of well-being [8]. To enhance gaze stability and to improve vestibule-ocular reflex, the patient performed x1 viewing [8]. Progressions to each exercise are described in Table 2 and were progressed as needed. These progressions involved changing the eyes, head movement, speed, movement amplitude, target location, target distance, foot position, base hardness, base width, and gait [8]. Other adaptation exercises included quick movements between two targets and smooth pursuits. Progressions were done in a similar fashion with the other exercises mentioned above. The patient was educated to delete on the principles of vestibular adaptation and habituation. The patient was instructed to perform gaze stability exercises four to five times daily for a total of 20 - 40 minutes a day and at least 20 minutes of posture and gait stability exercises [8]. The goals of postural stability exercises were to help the patient learn to use stable visual references and surface somatosensory information from their primary postural sensory system, use the remaining vestibular function, identify efficient and effective alternative postural movement strategies, and recover normal postural strategies [8]. The patient also received a home exercise program (HEP) to supplement the exercises performed within the clinic. He was instructed to perform his adaptation exercises two to three times a day for a total of 20 minutes a day and to perform at least 20 minutes of posture stability HEP exercises [8] [31]. At the beginning of each consequent therapy session, the patient was asked if he performed his exercises and was asked to demonstrate the activities to ensure compliance with the program.
Table 2. Exercises [8] [30].

<table>
<thead>
<tr>
<th>Gaze Stability</th>
<th>Eye</th>
<th>Open → Closed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Head movement</td>
<td>Horizontal → Vertical</td>
</tr>
<tr>
<td></td>
<td>Speed</td>
<td>Slow → Fast</td>
</tr>
<tr>
<td></td>
<td>Amplitude</td>
<td>Small → Large</td>
</tr>
<tr>
<td>Progression</td>
<td>Target location</td>
<td>Fixed → Moving → Imaginary → Full field</td>
</tr>
<tr>
<td></td>
<td>Target distance</td>
<td>Far → Near</td>
</tr>
<tr>
<td></td>
<td>Base hardness</td>
<td>Hard → Soft → Cushion</td>
</tr>
<tr>
<td></td>
<td>Base width</td>
<td>Wide → Narrow</td>
</tr>
<tr>
<td></td>
<td>Gait</td>
<td>Static → Walking</td>
</tr>
</tbody>
</table>

- X1 viewing: Gaze fixed on a stationary target with head moving in pitch and yaw plane.

<table>
<thead>
<tr>
<th>Eye Movements</th>
<th>Eye</th>
<th>Open → Closed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Head movement</td>
<td>Horizontal → Vertical</td>
</tr>
<tr>
<td></td>
<td>Speed</td>
<td>Slow → Fast</td>
</tr>
<tr>
<td></td>
<td>Amplitude</td>
<td>Small → Large</td>
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<tr>
<td>Progression</td>
<td>Target location</td>
<td>Fixed → Moving → Imaginary → Full field</td>
</tr>
<tr>
<td></td>
<td>Target distance</td>
<td>Far → Near</td>
</tr>
<tr>
<td></td>
<td>Base hardness</td>
<td>Hard → Soft → Cushion</td>
</tr>
<tr>
<td></td>
<td>Base width</td>
<td>Wide → Narrow</td>
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<tr>
<td></td>
<td>Gait</td>
<td>Static → Walking</td>
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</tbody>
</table>

- Active eye movements between two targets: While keeping the head still and only moving the eyes. Two targets are placed 2 ft apart from each other. The patient will look at one target and quickly looks at the other target without moving his head. This exercise is repeated several times.

- Smooth Pursuit: While keeping the head still and only moving the eyes. The patient extends one arm while holding a card (target) up. The patient is instructed to move their arm horizontally and vertically approximately 30° to the right and left and repeated again up and down.
At the 10th visit, the patient was reassessed. There were mild improvements in his FGA (FGA = 23) and ABCs (ABC = 80), although this score was not significant enough to claim a minimal detectable change. This further supports the article by Lee HJ [30], indicating that objective vestibular function and vestibular compensation will improve with eight weeks of continuous vestibular rehabilitation. There was a significant change in the patient’s DHI (DHI = 50) score at the 10th visit. The patient reported of having decreased dizziness intensity, frequency, and duration. At this point in time, the patient was participating in part-time stats at work. He also felt comfortable reading for 30 minutes and was excited to continue his improvement.

Following his follow-up, the patient was introduced to a virtual reality (VR) environment [3] [4] [14]. The goal for VR was continued challenges to his oculomotor and vestibular system with the intent to return to full-time work. The patient performed VR activities for 20 - 30 minutes and was instructed to inform the SPT if there were any changes in symptoms [14] [31]. The VR applications that were used included: Vanguard V, InMind VR, InCell VR, VR TunnelRace, Roller Coaster, and The Walk VR. Some of these applications were used with the idea that they were able to mimic movements and activities used in a VRT [12]. Vanguard V, InMind VR, InCell VR, and VR Tunnel Race were games that had the patient maintain static balance while dynamically moving his head into various head positions (pitch, yaw, and roll). These games mimic many of the movements that the patient performs during therapy. Each game has a mixture of optokinetic exercises with vestibular exercises because the game encourages head movement with a busy field of view [4]. VR also gave the SPT an opportunity to provide variety to the patient’s program. Another objective of the VR environment was decreasing the patient’s anxiety with heights that may simulate experiences in his line of work [13]. The Roller Coaster and The Walk VR apps were utilized to decrease the patient’s anxiety with heights following similarities of exposure therapy [19]. The Roller Coaster app is an application where a person is placed in a first-person view of a roller coaster ride. The quick movements and changing directions of simulator were used to help improve the patient’s visual systems. The Walk VR is a simulation of a person walking a tightrope be-

<table>
<thead>
<tr>
<th>Postural Stability</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Balance: Held for 30 second intervals.</td>
<td>Foot position</td>
</tr>
<tr>
<td>Eye Open → Closed</td>
<td>Shoulder width → Together → Tandum → Single leg</td>
</tr>
<tr>
<td>Speed Slow → Fast</td>
<td>Arm position</td>
</tr>
<tr>
<td>Amplitude Small → Large</td>
<td>Outstretched → Close to body → Across chest</td>
</tr>
<tr>
<td>Base hardness Hard → Soft → Cushion</td>
<td>Base width</td>
</tr>
<tr>
<td>Gait Static → Walking</td>
<td>Wide → Narrow</td>
</tr>
</tbody>
</table>
between the Twin Towers in New York. The patient began these activities on a firm surface and was progressed to varying surfaces and different stance positions. Due to the restrictions of the applications and concerns of safety, the patient remained static throughout all VR simulations.

6. Outcomes

At discharge, the patient reported feeling overall improvement since his initial evaluation. Improvements were seen in DHI, ABC, FGA, and SOT scores when compared to his initial evaluation. See Table 1 and Table 3 for more details. There were noticeable improvements during the performance of the FGA. The patient no longer demonstrated difficulties with walking with head movements, walking with a narrow base of support, and walking with eyes closed. Although there were improvements in backward ambulation, the patient revealed some difficulty. He was able to achieve all short and long term goals estimated during the plan of care. The patient expressed enthusiasm as to the improvement he achieved through his time in therapy. He described a significant decrease in the intensity, duration, and frequency of his dizziness symptoms since his evaluation.

The patient also had improvements in ICF model of activity and participation levels. For activity, the patient was able to read a book and his phone over an hour without reproduction of symptoms. He was able to demonstrate a normal gait pattern without a loss of balance or any deviations. His participation improved as he was able to return to work with full confidence. The patient also explained that he was able to drive for over 2 hours without any reproduction of symptoms. He described that he was able to participate in more family functions without any worries of losing his balance or an increase in dizziness episodes. He mentioned that the last time he had an episode of dizziness was two weeks ago when he was driving through a mountain pass. He explained that he was able to implement the activities he learned from therapy to quickly resolve any episodes of dizziness. It was recommended that the patient continue performing his vestibular exercises of ×1 viewing and smooth pursuits 3 times a day for a total of 20 - 40 minutes to help maintain optimal function [31].

7. Discussion

The purpose of this paper is to explore the use of VR as a viable tool for a balance program for a patient who is experiencing visual and vestibular impairments. The patient had improved ABCs scores from 75% to 95% at the time of Table 3.

<table>
<thead>
<tr>
<th>Table 3. DHI, ABC, SOT scores.</th>
</tr>
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<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>DHI</td>
</tr>
<tr>
<td>ABC</td>
</tr>
<tr>
<td>SOT</td>
</tr>
</tbody>
</table>

T1—Initial evaluation, T2—10th visit follow up, T3—Discharge.
discharge. The ABCs is an outcome measure where the patient rates their balance confidence in performing activities. The patient was able to change with an increase of 20 points to his initial evaluation. This demonstrates that the patient has more confidence in his balance with the help of VR and VRT. Research has shown that psychological factors such as anxiety from fear of falling are linked with decreased confidence with balance [19] [20] [33]. It can be inferred that the patient’s confidence in performing activities increased as the patient’s anxiety decreased while performing within VR.

Other studies have shown the benefits of a vestibular rehabilitation program in patients with balance deficits due to visual, somatosensory, and vestibular deficits [8] [30]. We have explored research regarding the use of VR technology to compliment exercises and activities within a vestibular rehabilitation program. These include gaze stability and smooth-pursuit eye movements as well as head positions achieved through various applications that are available [9] [12] [13]. The patient showed steady improvement when measured from baseline to his follow-up visit with DHI scores improving from 74 to 50. Following the application of VR into his rehabilitation program, his DHI scores continued to improve from 50 to 4 at discharge. DHI scores placed the patient from a severe vestibular dysfunction to a mild vestibular dysfunction. This supports research of active head movements within vestibular rehabilitation as well as within the VR environment [12] [13] [14]. Activity improvements were seen through his ability to drive longer than two hours without increased dizziness symptoms, being able to read for over one hour without a subjective increase in symptoms, and demonstrated the ability to walk down a hallway without walking into an object. The ABCs and DHI are a subjective assessment done by the patient.

Improvements in these psychological areas are transferred functionally and were assessed using the SOT and FGA. Initially, the patient received a composite score of 67 with deficits seen within the visual and vestibular systems. At discharge, the patient received a composite score of 80 with all of his balance systems falling within the normative values of those at his age. With FGA testing, the patient initially received a score of 21 which placed the patient below normative values indicating that he was a falls risk. At time of discharge, the patient scored a 29/30. This shows that the patient had a significant change in scores from initial evaluation to discharge. These increases in scores support research regarding the use of VR as a supportive tool for vestibular rehabilitation [14]. With these improvements, the patient was able to return to full-time status with his work and was able to participate in more family activities.

Clinical findings of this case support the use of VR as a potential tool in the treatment of patients suffering from balance deficits due to visual and vestibular deficits. This case has shown the effectiveness of VR in improving a patient’s confidence, vestibular function, and balance systems. These findings are significant, as there is limited research that is specific to vestibular rehabilitation and the use of virtual environments. As more VR technologies are being developed and become low-cost, it will be available for anyone to use [3] [4]. More research
will be needed to see the effectiveness of VR in the assistance in evaluating and treating patients.

Some limitations of this study include the technology available for this case. The accessories that were used in the case were a Vigica VR headset and an iPhone S5. Many of the applications used throughout each therapy session were free apps that were available on the iTunes App Store. There were limitations of control the therapist had as the patient performed his exercises in the virtual environment. Since many applications required a fee to gain access, there were difficulties in gearing task-specific activities to help the patient achieve their long-term goals. Another limitation with this particular set-up is the patient’s ability to interact with his virtual environment. With the current technology being used, the patient mostly played a passive role within VR. Some of the activities the patient engaged in placed the patient in a position where the patient can only look around as a video played. In more interactive video games, the patient can move their head and stare at an object for a certain time to perform an action or move their head to move the virtual avatar within the virtual world. The headset itself can be considered another limitation. Due to the size and added weight of the headset, there may be minor imbalances created as the patient was wearing it. With further development of VR technologies, we will gain access to more task-specific activities, improved control throughout various virtual environments, more cost-effective equipment, and more efficient ways to provide essential feedback.

An alternative explanation to the patient’s improvements may be due to his maintained compliance to his vestibular rehabilitation program. A study by Lee explains how vestibular rehabilitation may take up to 8 weeks before significant improvements show [30]. Following the 4th week of the patient’s therapy, the patient was introduced to VR activities on top of performing his usual vestibular exercises.

Areas for improvement include the patient performing VR activities alone to see the effectiveness of VR. It would have also been helpful if the patient was able to buy a VR headset so that he could perform VR exercises at home. If the clinic had better access to an improved VR experience, it would allow for greater control of activities the patient has engaged it. It will also enable the therapist to see what the patient sees which allows the therapist to provide various types of feedback to improve motor learning [34]. Another weakness was that this case did not fully follow the clinical practice guidelines. Clinical practice guidelines explain that patients suffering from an acute unilateral vestibular hypofunction will see improvements in vestibular function when receiving supervised vestibular rehabilitation therapy once a week for about 3 weeks along with a HEP [31]. More time was required for treatment since the patient did not feel he has reached his goals of therapy due to continued imbalance and gait deviations. A virtual environment was used to continue challenging his vestibular and visual systems so the patient would be able to return to full-time work status. The virtual world gave the therapist the ability to virtually simulate the patient’s work.
environment and to build the patient’s confidence [19]. Improved VR technology would give the therapist the ability to check for adherence of the patient’s HEP and allows the therapist to give more constructive feedback to their patient to improve scores [4]. As technology continues to advance, there will be improved control of variables within VR which can create a better immersive experience for all who participate [4]. Future research will be needed to see how VR stands to vestibular rehabilitation alone or both combined. A study like this will allow us to see if VR would work with vestibular rehabilitation as an adjunct activity.

In summary, the patient demonstrated significant improvements with vestibular rehabilitation and VR activities as evidenced by improved scores in ABCs, DHI, SOT, and FGA. Some of these applications allow for task-specific activities to allow the patient to engage in more meaningful interactions. The patient also expressed increased confidence in performing gait activities, returning to work, and engaging in more family activities at home. These improvements can be attributed to the combination of vestibular rehabilitation and VR exercises. This case report provides valuable information regarding the use of VR as an intervention technique to improve postural balance in individuals suffering from visual deficits and unilateral vestibular hypofunction impairments.

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The Relationship between Consumption of Fast Food with Level of Serum Folate among Nursing Students of Islamic Azad University, Tehran Medical Sciences Branch in 2016

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Abstract

In recent decades, substantial increase in average weight of individuals has been seen in rich countries. Such changes are the result of significant changes in pattern of people’s lives. One of these issues is increasing levels in consumption of fast foods or processed foods. According to experts, the consumption of processed foods, because of having high-calories and trans-fatty acids, is fattening and harmful. In this study, the researchers after obtaining permission from the ethics committee and head of the School of Nursing, introduced themselves to nursing students then, samples were randomly selected among those who are eligible for the study. Before performing to complete the questionnaire and relevant experiments, testimonial were asked from the subjects. At the end of the study, results were suggested that, levels of Serum folate between males and females and also among married and single people were equivalent. Level of Serum folate among those students who usually have anemia in their families is significantly lower than those ones who have not anemia in their families (P = 0.003). There was a significant relationship between age and semester with levels of folate (P < 0.05); i.e. by increasing age and educational terms, levels of serum folate would be reduced. The level of serum folate among students who smoke is lesser than those do not (P = 0.001).

Keywords

Fast Food, Serum Folate, Nursing Students

1. Introduction

Anemia is one of the most common health problems which according to the
World Health Organization, is more common in South Asia and Africa compared to the rest of the world [1]. Nutritional anemia is a major problem around the world especially in developing countries. Although iron-deficiency anemia is the most common cause of anemia; however, lack of vitamins such as B6, B12 and folic acid is also causing anemia. These micronutrients are affected directly by the increasing hemoglobin synthesis or indirectly by rising absorption of iron [2]. Studies show, increasing consumption of fast foods is related with getting more energy and obesity and also with less consumption of fruits, vegetables and healthy foods among children, adolescents and adults. Increasing the proportion of high-fat diets and high amount of energy such as fast foods along with reducing physical activities and doing works in sitting status and also lack of movement is some of important factors for gaining weight. Most of people in order to overcome emotion, stress and anxiety problems are overeating. Meantime, students, because of special circumstances, are capable of facing with stress, anxiety and poor dietary patterns (processed foods). Each of these factors can cause changes in their healthy lives [3]. By increasing rate of anemia caused by iron and folic acid deficiency and also financial crisis, the role of lifestyle modification including nutrition is more considerable than before [4].

2. Methodology

This research was descriptive-correlational that shows the relationship between fast food consumption with levels of serum folate. Descriptive-correlational is a study that the researchers clearly define the variables without any interference or manipulation of them. In other words, it is a study in which the researchers try to discover and define the relationship among variables [5]. In this study, the researchers selected randomly their samples among nursing students of Islamic Azad University of Tehran Medical Sciences branch who had eligible criteria for the study of October 2015 until December 2016, testimonial were asked from the subjects, then at the presence of the researcher questionnaires were completed. Questionnaire was inclusive three branch principal: Introduce characteristic, present illness history, nutrition and meat habits. In cases where students were academically busy, researcher went to School of Nursing or subordinate hospital of Islamic Azad University of Tehran Medical Sciences branch in other times in order to collect the questionnaires. After completing the questionnaires, blood samples were taken for testing folate among those students, who met the criteria for the study, then, the samples were sent to Bu-Ali Hospital laboratory (subordinate to Islamic Azad University of Tehran Medical Sciences branch)and level of folate serum were tested. The time of testing was at a particular time and day and also at the presence of the researchers. After collecting the questionnaires and getting the answer of tests, they were analyzed at the next step. Data analysis was done by SPSS v. 20. Descriptive statistic (frequency, mean, standard deviation) and inferential tests (independent T, Pearson correlation coefficient, ANOVA and Scheffe post hoc test) methods were used.
3. Findings

In this chapter, collected data were analyzed. In order to describe data, statistical indicators such number, percent, minimum, maximum, mean and standard deviation are used; and for data analysis t-test, Pearson correlation coefficient, ANOVA and Schiff post hoc test were applied. Relationships between consumption of processed foods with levels of folate serum have been studied among nursing students of Islamic Azad University. The population sample was about 100 students (34 males and 66 females) that are randomly selected among students of mentioned School on academic year of 2016. Table 1 shows the demographic information results. Table 2 shows the Correlation of folate serum level with monthly consumption of fast food and Table 3 shows Mean and SD of folate serum levels among nursing students also Table 4 shows Correlation between levels of folate serum with age, academic semester, height, weight and BMI.

Table 1. Absolute and relative frequency distribution among nursing students of Islamic Azad University, Tehran Medical Sciences branch in year of 2016.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>34 (34)</td>
</tr>
<tr>
<td>Female</td>
<td>66 (66)</td>
</tr>
<tr>
<td>Marital Status</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>30 (30)</td>
</tr>
<tr>
<td>Married</td>
<td>70 (70)</td>
</tr>
<tr>
<td>Semester</td>
<td></td>
</tr>
<tr>
<td>Three</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Four</td>
<td>18 (18)</td>
</tr>
<tr>
<td>Five</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Six</td>
<td>27 (27)</td>
</tr>
<tr>
<td>Seven</td>
<td>29 (29)</td>
</tr>
<tr>
<td>Eight</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Employment Condition</td>
<td></td>
</tr>
<tr>
<td>No-Job</td>
<td>57 (57)</td>
</tr>
<tr>
<td>Labor</td>
<td>15 (15)</td>
</tr>
<tr>
<td>Employee</td>
<td>16 (16)</td>
</tr>
<tr>
<td>Self-Employed</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Residency Status</td>
<td></td>
</tr>
<tr>
<td>With Family</td>
<td>58 (58)</td>
</tr>
<tr>
<td>Dorm</td>
<td>24 (24)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Yes</td>
<td>90 (90)</td>
</tr>
<tr>
<td>Alcohol Drinking</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>14 (14)</td>
</tr>
<tr>
<td>Yes</td>
<td>86 (86)</td>
</tr>
<tr>
<td>Having Specific Disease</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Yes</td>
<td>93 (93)</td>
</tr>
<tr>
<td>Records of Anemia</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>14 (14)</td>
</tr>
<tr>
<td>Yes</td>
<td>86 (86)</td>
</tr>
</tbody>
</table>
Table 2. Correlation of folate serum level with monthly consumption of fast food among students of Islamic Azad University, Tehran Medical Sciences branch in year of 2016.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mess Code</th>
<th>Correlation Coefficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamburgers</td>
<td>100</td>
<td>-0.257</td>
<td>0.01</td>
</tr>
<tr>
<td>Sausage, Salami and Ham</td>
<td>100</td>
<td>-0.368</td>
<td>0.0001</td>
</tr>
<tr>
<td>Chicken Nuggets</td>
<td>100</td>
<td>-0.12</td>
<td>0.235</td>
</tr>
<tr>
<td>Fish and Fried Shrimp</td>
<td>100</td>
<td>-0.186</td>
<td>0.064</td>
</tr>
<tr>
<td>Chips, Fries</td>
<td>100</td>
<td>-0.384</td>
<td>0.0001</td>
</tr>
<tr>
<td>Pizza</td>
<td>100</td>
<td>-0.401</td>
<td>0.0001</td>
</tr>
<tr>
<td>Spaghetti and Pasta</td>
<td>100</td>
<td>-0.207</td>
<td>0.039</td>
</tr>
<tr>
<td>Sweets</td>
<td>100</td>
<td>-0.342</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mayonnaise Souse</td>
<td>100</td>
<td>-0.205</td>
<td>0.041</td>
</tr>
</tbody>
</table>

Table 3. Mean and SD of folate serum levels among nursing students of Islamic Azad University, Tehran Medical Sciences branch in year of 2016.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Gender</th>
<th>Mess Code</th>
<th>M</th>
<th>SE</th>
<th>T</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folate Serum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>34</td>
<td>5.89</td>
<td>5.81</td>
<td>0.07</td>
<td>0.944</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>66</td>
<td>5.97</td>
<td>5.39</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>70</td>
<td>5.91</td>
<td>5.4</td>
<td></td>
<td>0.103</td>
<td>0.918</td>
</tr>
<tr>
<td>Married</td>
<td>30</td>
<td>6.03</td>
<td>5.85</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With Family</td>
<td>58</td>
<td>5.38</td>
<td>5.57</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorm</td>
<td>42</td>
<td>6.72</td>
<td>5.39</td>
<td></td>
<td>1.23</td>
<td>0.932</td>
</tr>
</tbody>
</table>

Smoking

| Folate                          | Yes    | 1.89 | 2.92| 4.1 | 0.001 |
| No                             | 90     | 6.35 | 5.55|     |       |

Alcohol Drinking

| Folate                          | Yes    | 6.2  | 5.52|     | 0.185 | 0.854 |
| No                             | 86     | 5.9  | 5.54|     |       |       |

Records of Other Disease

| Folate                          | Yes    | 6.01 | 6.47|     | 0.034 | 0.973 |
| No                             | 93     | 5.94 | 5.47|     |       |       |

Records of Anemia in Family

| Folate Serum                    | Yes    | 2.52 | 3.82|     | 3.35  | 0.003 |
| No                             | 86     | 6.5  | 5.55|     |       |       |

Job Condition

| Folate                          | Student| 6.28 | 0.69|     |       |       |
| LABOR                           | 15     | 6.64 | 5.8 |     | 0.454 | 0.653 |
| Employee                        | 16     | 5.26 | 4.95|     |       |       |
| Self Employed                   | 12     | 4.39 | 5.25|     |       |       |
Table 4. Correlation between levels of folate serum with age, academic semester, height, weight and BMI (body mass index) among nursing students of Islamic Azad University, Tehran Medical Sciences branch in year of 2016.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mess Code</th>
<th>Correlation Coefficient</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>100</td>
<td>-0.227</td>
<td>0.023</td>
</tr>
<tr>
<td>Academic Semester</td>
<td>100</td>
<td>-0.23</td>
<td>0.021</td>
</tr>
<tr>
<td>Height</td>
<td>100</td>
<td>0.075</td>
<td>0.458</td>
</tr>
<tr>
<td>Weight</td>
<td>100</td>
<td>0.141</td>
<td>0.16</td>
</tr>
<tr>
<td>BMI</td>
<td>100</td>
<td>0.125</td>
<td>0.216</td>
</tr>
</tbody>
</table>

Ahmadi Khatir (2015) investigated the relationship between consumption of fast food with anemia in patients. The study was done over 100 patients who came to subordinated hospitals of Mazandaran University of Medical Sciences. The average age on that study was about 29 years-old while on the present is 22 years-old. According to Table 4, 70% of the subjects in our study were single, while this amount was about 33 percent in Ahmadi Khatir study. In our study the average body mass was about 22.55; however, this amount was about 24 in Ahmadi Khatir study; i.e. the average body for majority of the participants in both studies were within the normal range of 25 to 18.5. In Ahmadi Khatir study, 86 percent of subjects were lived in the city and 14 percent were in rural areas; however, in our study, all subjects, i.e. 100 percent of them were lived in the cities.

Farzaneh et al. [6] have done a study to examine the consumption of fast food among students of Khalkhalcity, EA, Iran. The numbers of participants were 150 people, of which 28% were male and 72 percent were female; while, of 100 subjects in the present study 66% were female and 34% were male.

The findings of Shojaeian et al. [7] in their study “comparison of folate serum among pregnant women with and without preeclampsia” showed that there is a meaningful differences in folate serum ($P = 0.001$). The average amount of folate serum in patients without preeclampsia were about 1.42 ng per liter and in the group with preeclampsia were 0.87 ng per litre, but the mean for folate serum was about 5.94 in present study. Masoud et al. [8] have done a research to evaluate levels of folic acid serum in patients with/without ischemic stroke. This study has been done over 40 patients with cerebral stroke and 40 healthy persons. The average level of folic acid serum in patients with cerebral stroke was about 8.40 and for healthy group was 10.87; which this average was higher than of ours study. In a study conducted by Saboktakin et al. [9] on 70 patients with depression Folate deficiency was observed in 51.4 percent of subjects. But in the present study, folate deficiency was observed in 53 percent of subjects. This study was conducted over 100 nursing students.

4. Conclusion

Levels of folate serum are equal in males and females and also in married and single people. Levels of folate serum in students that in their families anemia ex-
ist, are significantly lesser than those who do not have anemia in their families ($P = 0.003$). No statistically significant relationships between age and academic semesters with levels of folate have been observed ($P < 0.05$); by aging and passing educational semesters, levels of folate serum are reduced. Also, levels of folate serum in students who smoke were lesser than those do not smoke ($P = 0.001$).

**Suggestions for Further Studies**

1) Examining factors such as vitamins in B group in a similar study;
2) The relationship between consumption of processed food with levels of folate serum among non-healthy (patients) group;
3) The knowledge and attitude of students towards fast food;
4) The effect of fast foods and reduction of folic acid on mental health;
5) The relationship between consumption of fast foods and gaining weight;
6) Evaluation of folate serum amount among individuals.

**References**


Overview of the Prevalence and Associated Risk, Factors of Lifestyle Diseases in University Students

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Abstract

**Background:** The prevalence of lifestyle diseases is increasing rapidly in Youths (17 - 25 yrs). Factors such as poor diet, little or no physical exercise, and smoking are major contributors to this increase. Lifestyle diseases in youths present a timeline challenge as disease duration is longer and financial burden more costly. **Aim:** To analyse and synthesize published literature on the prevalence of and risk factors associated with four lifestyle diseases—obesity, hypertension, diabetes and cancer—in university/college students worldwide. **Results:** The literature indicates that among lifestyle diseases in university/college students, overweight/obesity (Body Mass Index > 25 kg/m²) had the highest prevalence of 45.6% and duration of approximately 5 years. Cardiovascular diseases and hypertension had lower prevalence rates but prehypertension which lingers >4 years was at 32.0%. Type 1 diabetes mellitus (T1DM) had a fairly high prevalence in college students (21.7%); type 2 diabetes mellitus (T2DM) was found in much lower percentage (12.95%). Cancer had the lowest prevalence of >2% but was increasing in most regions based on the presence of multiple risk factors. **Conclusion:** Increase prevalence of these diseases in youths indicates that young people are at high risk of developing these diseases due to poor early lifestyle habits. Early corrective measures can reduce the burden of many lifestyle diseases.

**Keywords**

DM1 (Diabetes Mellitus Type 1), DM2 (Diabetes Mellitus Type 2), WHR (Waist-Hip Ratio), Obesity, World Health Organization (WHO)

1. Introduction

The overview will look at the percentage prevalence of four major diseases—obesity/overweight, hypertension, diabetes and cancer in university/college stu-
The review will look at percentage prevalence across different regions worldwide including: Africa, Europe, Asia, and South America, the United States and the Caribbean. Results will include both an individual percentage for different universities in each region and also an average percentage prevalence for each disease. The targeted population is university students which are usually between the ages of 17 - 30 years. Each year there is an increase in percentage prevalence for lifestyle diseases due to continued bad lifestyle habits such as poor diet and lack of exercise. The overview will give a general idea of what current statistics are in relation to the four lifestyle diseases outlined and the progression of each.

A lifestyle disease is defined as a non-communicable disease that is developed from unhealthy lifestyle choices that are related to smoking, alcohol, drugs and exercise. Lifestyle diseases include but are not limited to diabetes, obesity, cardiovascular diseases and some forms of cancers [1]. According to the WHO non-communicable diseases (NCD) account for over 36 million deaths each year. NCD deaths include cardiovascular diseases (17.3 million), cancers (7.6 million) and diabetes (1.3 million), all of which are categorized as lifestyle diseases [1].

Alwan indicated that lifestyle diseases are responsible for 63% of deaths globally as at 2008 with 80 percent of deaths taking place in low and middle-income countries [2] [3]. Among these lifestyle diseases, obesity, diabetes and cardiovascular diseases are major contributors to death.

Obesity and overweight are defined by WHO as abnormal or excessive fat accumulation that may impair health [4]. Body mass index (BMI) is used as an indicator for determining obesity. BMI uses a ratio of weight and height measurement and is defined by a person’s weight in kilograms divided by the square of height in meters (kg/m²). According to WHO, a BMI greater than or equal to 30 is considered as obesity while overweight is greater than or equal to 25 [4].

WHO defines cardiovascular diseases as any disorders of the heart and blood vessels, which includes, rheumatic heart disease, cerebrovascular disease (stroke), raised blood pressure (hypertension), peripheral artery disease, coronary heart disease (heart attacks), congenital heart disease and heart failure. Tobacco use, physical inactivity, an unhealthy diet and harmful use of alcohol are proposed to be the major causes which are all lifestyle related [5].

Another lifestyle related NCD is Diabetes which is defined by WHO as a chronic disease, which occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces causing an increase in the concentration of glucose in the blood (hyperglycaemia).

Three main types of diabetes exist:

Type 1 diabetes (previously known as insulin-dependent or childhood-onset diabetes) is described as a lack of insulin being produced. Type 2 diabetes (formerly called non-insulin-dependent or adult-onset diabetes) occurs as a result of the body not being able to effectively use the insulin it produces. Excess body weight and physical inactivity are usually the major causes for its development.
Gestational diabetes, the third type, is characterized by hyperglycaemia in pregnancy [6].

However, only two types: Type 1 and Type 2 diabetes mellitus will be considered for this review.

Method

2. Prevalence of Lifestyle Diseases

Prevalence of lifestyle diseases is rapidly increasing worldwide and according to the World Health Organization (WHO), non-communicable diseases are now the leading cause of death around the world (2011). NCDs of high significance include cardiovascular diseases, obesity and diabetes. The rise in prevalence of lifestyle diseases is due to tobacco use, poor diet and harmful use of alcohol [7].

2.1. Cardiovascular Diseases

Of NCDs cardiovascular diseases account for the most deaths with 17.3 million people dying annually [1]. In a study on university students in Sao Paulo, Brazil, risk of developing cardiovascular diseases was characterized mainly by a family history of the disease. There was 44.6% prevalence in such case while smoking and physical activities showed less prevalence; 10.7% and 35.7% respectively. Also lipid levels which gives an indication of development of cardiovascular disease showed prevalence in high total cholesterol and LDL-c levels as 16.1% and 5.4% respectively, while decreased HDL-c levels and increased triglyceride levels both showing 8.9% prevalence [8].
Similar study at the University of Talca, Chile showed a 12.8% prevalence of some degree of arterial hypertension among student which showed greater severity in men. Physical activity was much less in Chile with 91.5% of student not participating in any major physical activity while there was a much greater percentage of smokers (39.8%). Hypercholesterolemia was also seen in students with a 20.2% prevalence. 35.2% had cholesterol concentration of 200 - 210 mg/dl and 40.9% had concentrations of 221 - 230 or greater [9].

Hypertension In a study done on college students at the University of New Hampshire as much as 60% of males had high blood pressure/hypertensive [10]. However, lower incidence was seen in a descriptive study on undergraduate students in Lubango-Angola. Hypertension had a much lower prevalence among students with a 26.7% prevalence [11].

Further research done on both prehypertension and hypertension in college students in Kuwait defined prehypertension as systolic pressure between 120 and 139 mm Hg or diastolic pressure between 80 and 89 mm Hg. Results showed that none of the subjects were hypotensive. Of the participants 39.5% were prehypertensive and 7% were considered hypertensive. Other tests were done simultaneously including lipid test and an oral glucose tolerance test. Finding showed a linkage between BMI determined Obesity, high HDL and cholesterol level; all of which are lifestyle dependent [12].

2.2. Obesity/Overweight

Overweight and Obesity is a growing trend in students and adults across the world. Poor diet and exercise being the most significant contributing factors. In a study in Sao Paulo on first year university students, research shows that the prevalence of overweight and obesity was as high as 17.8% and 7.1%, respectively. Additional data showed that individuals consumed an inadequate diet which was high in fat and protein but low in dietary fibre and carbohydrates. Consumption of a high quantity of fat among students is indicative of the percentage overweight and obesity found in the study [8]. An even higher percentage of overweight and obesity was seen in a study on university students in south central Chile. Results show a prevalence of 45.5% in men and 24.3% in women. In men the percentage represents almost half of the sample size. A reason for this was that most of the men sampled was involved in a little or no physical activities or had poor diets. Also measurement of WHR using >102 cm for men and >88 cm for women as the cut-off point it was seen that 12.8% of both males and females had a value greater than the normal [9].

One method that is commonly used to determine Obesity is the Body Mass Index (BMI). This method was used in a study on obesity among male university students in the United Arab Emirates. Non-obese students were classified as students with a cut-off of <25 while obese students were ≥25. The prevalence of obesity in male students was 35.7%. There was a relative risk (RR) of 1.88 for students who had a family history of obesity/overweight or one of the other three lifestyle diseases. Relative risk was also seen in smokers and persons not
practicing sports. However, a family history was the only statistically significant risk factor [13].

Similarly, Iran University of Medical Sciences used the BMI bivariate analysis. For this study, BMI was used to classify persons as non-obese (BMI less than 25 kg/m²) and as obese (BMI ≥ 25 kg/m²). Mean BMI for all subjects was 21.7 ± 2.9 kg/m². Almost 88% of the subjects were classified into a non-obese group (BMI < 25 kg/m²). About 10% were underweight and 12.4% of the students had a BMI more than 25 kg/m²). The sample therefore shows that most individuals were considered as non-obese since the mean BMI was in the normal range [14]. In contrast, Stack et al. had an average BMI that would be considered in the overweight category having an average BMI of 26.81 ± 0.75 kg/m² but the population studied was not overweight [15].

Further research classified obesity into grade 1 and 2 (BMI > 25 and >30 kg/m²). Prevalence of grade 1 and 2 obesity was found to be 32.0 and 8.9%, respectively. Factors that were found to be significantly associated with obesity included gender, age, marital status, obesity among parents, dieting, last physical check-up, year of study, regular meals eaten and high school GPA [16].

Research by Huang et al. used similar criteria (BMI > 25 and >30 to classify obesity). The results showed overweight prevalence of 21.6% using BMI directly and 16.2% using BMI percentile while obesity prevalence was 4.2% using BMI percentile and 4.9% using BMI directly. It was seen that assessment using direct BMI measurement gave higher percentage of both overweight and obesity. The BMI percentile uses comparison between other individuals in the sample and therefore gives a better indication of obesity prevalence [17].

Study on more than 800 college students at the University of New Hampshire in a general nutrition course found that approximately one-third (1/3) of the sample size was either overweight or obese. The results also included metabolic syndrome which is a cluster of five risk factors (low HDL, excess abdominal fat, high triglycerides, high blood pressure and high blood glucose). In males prevalence of metabolic syndrome was as much as sixty-six percent and fifty percent in females having at least one of the risk factors. Eight percent of males had all five [10].

Another research surveyed 738 college students aged 18 to 27 years to assess overweight, obesity, dietary habits, and physical activity. They used BMI (body mass index) > 25 kg/m² or BMI > 85th percentile and BMI > 30 kg/m² or BMI > 95th percentile to estimate overweight and obesity in those aged < 19 years. To define overweight and obesity in those >20 years, they used BMI > 25 kg/m² and >30 kg/m². They found overweight rates of 21.6% using BMI directly and 16.2% using BMI percentile and obesity rates of 4.9% using BMI directly and 4.2% using BMI percentile. More than 69% of the participants reported consuming < 5 servings of fruits and vegetables per day and more than 67% reported consuming < 20 g of fibre per day. Also of significance participants reported physical activity on fewer than 3 days per week. Most college students were not meeting the required diet and physical activity levels.
2.3. Diabetes

Diabetes is usually in the form of Type 1 in Youths, however few cases of Type 2 exists. In college students the prevalence of diabetes varies based on sex, socioeconomic and socio-demographic factors. Study on a group of college students in south Texas shows high prevalence of diabetes or at risk of developing diabetes, 21.7% of subject showed elevated reported risk while 4.3% of subjects had a moderate-to-high risk of developing diabetes [15]. Much lower percentage of Type 2 diabetes was seen in another study on 702 students in Fortaleza, Brazil. 10.2% of males and 15.7% of females had high glucose levels. 13.8% of subjects between ages 16 - 19 had elevated levels which decreased in ages 20 - 24 (11.9%) and 25 - 28 (10.7) [11].

On the other hand, a study in south India on a group of over 3000 students between ages 5 - 19 using oral glucose tolerance test found that there was no case of diabetes of any kind despite 8.6% of subjects having a family history of the disease [18].

2.4. Cancer

Although there is not much research done on prevalence of cancer in children or youths research shows increasing risk of developing cancer due to lifestyle choices. Research on Northwest University students showed that a large percentage of the subjects were not eating the required amount of fruits and vegetables (95%) while 60% were not getting enough physical activities; two risk factors that increase risk of developing the disease [19]. Study also found a relationship between obesity and cancer. In women, 20% of cancer-associated deaths were caused by obesity. In one such case overweight or obesity can increase the chance of getting breast cancer by creating a cancer-friendly environment through fat cells [19].

2.5. Significance of the Findings

The four lifestyle diseases varied in prevalence in university/college students. Obesity and overweight was the most common lifestyle disease found in youth. Percentages of overweight were generally much higher than obesity. However, lack of exercise, poor diet and other bad health practices on a regular basis can cause overweight individuals to become obese. High percentages of overweight (45.5%) increase the chance of more individuals becoming obese with time. Of note, males studied showed greater prevalence than females due to the fact they were also less physical and were more involved in alcohol consumption and smoking. In all cases of overweight and obesity there was trend of WHR values being over the normal (>102 cm for males and >88 cm for females, as much as over 12% in some cases. Type 1 diabetes also had high prevalence in college students but lower prevalence in comparison to overweight and obesity. Type 2 diabetes had similar prevalence as type 1 diabetes. However, it is expected that type 2 diabetes would have very low percentage since it is uncommon in the age group but a family history of the disease and bad health practices gives reason for such findings. In contrast to overweight and obesity females had higher per-
centages as well as a study found no incidence of diabetes in one case. Hypertension generally had lower prevalence than obesity in most cases but higher prevalence than type 1 or type 2 diabetes. However, one study found as much as 60% of males having hypertension. Pre-hypertension was found in high percentage (up to 39.5%), subjects which were pre-hypertensive had bad lifestyle choices which may result in hypertension with time. Cancer prevalence in college/university students is not as high as the other three lifestyle related diseases but research shows increasing risk of students developing cancer due to poor diet and lack of exercise. Both can also cause individuals to become overweight or obesity which is link to cancer especially in women.

3. Conclusion

In most of the studies done on college/university one or more lifestyle diseases were found in the sample. Obesity and overweight was the most prevalent with consistently high percentage in each study. Similarly hypertension and pre-hypertension showed high prevalence while diabetes have low prevalence in comparison. Cancer was not prevalent but shows high risk of development in students. Finding indicates the need for interventions in developing strategies which targets bad lifestyle choices and therefore reducing the risk of developing such diseases.

Showing the average estimated percentage prevalence of cancer and three other lifestyle diseases across four regions.

<table>
<thead>
<tr>
<th>Diseases</th>
<th>North America</th>
<th>Europe</th>
<th>Asia</th>
<th>Africa</th>
<th>Caribbean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>2.3% [22]</td>
<td>2.45% [22]</td>
<td>1.47% [22]</td>
<td>0.64% [22]</td>
<td>0.2% [22]</td>
</tr>
</tbody>
</table>

The rate of cancer in university students is similar in Europe and North America, no significant difference was seen between these two regions. The Caribbean had the lowest cancer rate (0.2) followed by Africa (0.6%) and Asia (1.47%). A Significant difference in cancer rate was seen between Africa and Europe and Asia and Europe ($P < 0.05$).

Showing the associated risk factors of each lifestyle disease reviewed.

<table>
<thead>
<tr>
<th>Lifestyle Diseases</th>
<th>Associated Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity/Overweight</td>
<td>Poor diet (high in fat and protein but low in dietary fiber and carbohydrate), little or no exercise, smoking &amp; family history of the disease [8] [9] [10].</td>
</tr>
<tr>
<td>Hypertension/Cardiovascular Disease</td>
<td>Smoking, Lack of exercise, family history of the disease and diet high in fat [8] [9] [19].</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Diet high in sugar and fat, lack of exercise, family history of the disease [18] [20].</td>
</tr>
<tr>
<td>Cancer</td>
<td>Diet lacking fruits and vegetables, obesity, family history of the disease lack of physical activities [21].</td>
</tr>
</tbody>
</table>
References


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