Higher Serum Potassium Level Associated with Late Stage Chronic Kidney Disease

Ming-Fang Hsieh, MD; I-Wen Wu, MD; Chin-Chan Lee, MD; Shun-Yin Wang; Mai-Szu Wu, MD

Background: The serum potassium (K⁺) level is kept in a narrow range to sustain normal physiology within the human body by the kidneys. The serum K⁺ level in different stages of chronic kidney disease (CKD) remains undefined.

Methods: We conducted a cross-sectional study to observe the serum K⁺ level in patients without clinical manifestations of hyperkalemia in the late stages of CKD (stages 3-5). A total of 531 patients with late stage CKD were included and followed up for at least 1 year, from March 2006 to May 2007. The patients were sub-grouped by stages of CKD, which were determined by a “Modification of Diet in Renal Disease” equation estimating the glomerular filtration rate (eGFR). The serum creatinine, eGFR and K⁺ levels were recorded at least twice during the study. We analyzed the average K⁺ level in these late-stage CKD patients.

Results: The average K⁺ level increased along with renal function deterioration in the late stages of CKD (stage 3: 4.36 ± 0.49; stage 4: 4.50 ± 0.55; stage 5: 4.69 ± 0.73 mEq/L, p < 0.05). Men and patients with diabetes mellitus, a low eGFR, and a low hemoglobin might have higher levels of serum K⁺. We also noticed that there was a linear increase in the standard deviation of the serum K⁺ level as renal function deteriorated. The use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers was not associated with hyperkalemia in our patients.

Conclusion: Our results reflected that the serum K⁺ level increased in correlation with the decline in the eGFR in the late stages of CKD. Also, male gender, diabetes mellitus, and anemia might be risk factors for higher K⁺ levels in CKD patients. The variation in the serum K⁺ level became wider as renal failure progressed.

(Chang Gung Med J 2011;34:418-25)

Key words: chronic kidney disease, hyperkalemia

Potassium (K⁺) is the most abundant cation within intracellular fluid. The serum K⁺ level is the major factor in determining the cellular resting potential, which is important for excitable cells such as neurons and myocardial cells.(1,2) An elevated serum K⁺ level is a medical emergency in daily prac-
tice because of its rigorous alteration of cardiac electrophysiology. An elevated serum K+ level is associated with reduced myocardial conduction velocity and accelerated repolarization. Extreme values in hyperkalemia can even lead to fatal cardiac arrhythmias. (3)

The serum K+ level is maintained within a very narrow range in the human body. The redistribution of K+ between the intracellular and extracellular space can equilibrate the serum K+ level from the daily intake of K+. However, the most important part of long-term K+ regulation depends on renal K+ excretion. (1) Secretion of K+ occurs mainly in the cortical collecting ducts, in which a family of apical membrane K+ channels the renal outer medullary K+ channels (ROMK), in the principal cells efficiently excrete surplus K+. (4-6) The ability of the kidney to excrete K+ keeps our internal milieu out of danger from complications associated with high K+ levels. Also, the serum K+ level is one of the major regulators in renal K+ excretion. A high serum K+ level leads to enhanced ROMK activity and increased renal K+ excretion. (8)

The mechanism of renal excretion of K+ is compromised in patients with chronic kidney disease (CKD). The serum K+ level might increase along with deteriorating renal function. Subsequently, the elevated K+ level might by itself stimulate K+ excretion. A new steady state develops without medical complications. (9) It is reasonable to speculate that the elevated serum K+ level might be a physiological adaptation of a failing kidney. It is interesting to question what is an acceptable range of the serum K+ level in patients with different degrees of kidney dysfunction. We hypothesized that the K+ level increases along with deterioration of renal function within a range different from that of patients with normal renal function. We conducted a retrospective observational study to evaluate the relationship of serum K+ levels and renal function in the late stages of CKD.

METHODS

Study population

In this study, we initially included 592 predialysis CKD patients, who visited the nephrology outpatient clinics of the Department of Nephrology at a university-affiliated teaching hospital, Chang Gung Memorial Hospital in Keelung from March 2006 to May 2007. Patients from 18-80 years old who participated in a multidisciplinary predialysis education program were included after obtaining informed consent. Nine patients discontinued follow-up and thirty five patients who had documented cardiac arrhythmias or were under current or recent (in the previous 6 months) treatment with cation exchange resins, diuretics, β-blockers, digoxin, mineralocorticoids, or non-steroidal anti-inflammatory drugs were excluded from the study. (8,9) A total of 548 patients received standardized predialysis education and counseling from a dietician according to guidelines of The National Kidney Foundation/Kidney Disease Outcomes Quality Initiative.

Definition of CKD

CKD was defined as a structural or functional kidney abnormality persisting for at least 3 months and manifested by either kidney damage (persistent proteinuria) or a decreased estimated glomerular filtration rate (eGFR) (< 60 mL/min per 1.73 m²), as estimated by the abbreviated Modification of Diet in Renal Disease equation in which the estimated GFR = 186.3 x (serum creatinine level) –1.154 x age –0.203 x (0.742 if female). (10) For descriptive purposes, CKD stage 1 was defined as eGFR > 90 mL/min per 1.73 m² with structural abnormalities or proteinuria; stage 2, as 60 to 89 mL/min per 1.73 m²; stage 3, as 30 to 59 mL/min per 1.73 m²; stage 4, as 15-29 mL/min per 1.73 m² and stage 5, as < 15 mL/min per 1.73 m² or commencement of dialysis therapy. We also showed the patients’ GFR calculated by Cockraft-Gault method in which the estimated GFR = (140-age) x (Weight in kg) x (0.85 if female) / (72 x Cr (mg/dL)).

Laboratory and clinical data

Blood was collected in the morning after overnight fasting. The serial measurement of K+ was performed in the core laboratory of Chang Gung Memorial Hospital using the a Synchron LX System (Synchron LX ISE, Beckman Conlter, Inc. Fullerton, CA, U.S.A.) with a normal range value of 3.0 to 4.8 meq/L. Information obtained from each patient included age, gender, body mass index (BMI), comorbidity, and usage of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) for more than one year. Comorbidity included diabetes, hypertension, hyper-
lipidemia, chronic glomerulonephritis, cerebrovascular attack and coronary artery disease. Chronic glomerulonephritis was diagnosed clinically or pathologically, and coronary artery disease was impressed according to coronary angiography. Concentrations of serum K⁺, sodium, chloride, calcium, phosphate, serum creatinine and hemoglobin were checked at least twice in the follow-up period. The average K⁺, sodium, chloride, calcium and phosphate levels were used for investigation in this study. Hyperkalemia was defined as an average serum K⁺ value > 4.8 meq/L. The first serum creatinine levels were used for eGFR and analysis.

**Statistical methods**

Descriptive statistics were expressed as mean and standard deviation. Discrete variables were presented as frequencies and group percentages. All variables were tested for normal distribution by the Kolmogorov-Smirnov test. Student’s t-test was applied to compare means of continuous variables and normal distribution data. Categorical data were tested using the chi-square test. Analysis of variance using the least significant difference post hoc test was used for numerical values. Risk factors for hyperkalemia with statistical significance in the univariate analysis were included in multivariate analysis by applying a multiple logistic regression based on backward elimination of data. All statistical tests were two-tailed, and \( p < 0.05 \) was considered statistically significant. Data were analyzed using SPSS 13.0 for Windows XP (SPSS, Chicago, IL, U.S.A.).

**RESULTS**

**Baseline characteristics**

A total of 592 patients were enrolled in the study. Five-hundred eighty three patients completed laboratory analyses and only 548 patients completed the 12-month follow-up. After excluding seventeen patients with early stage (stage 1 and stage 2) CKD, 531 patients were included in our study. Patient’ characteristics are summarized in Table 1. There was a trend showing an increase in serum K⁺ levels along with a progression of renal function. The K⁺ levels were significantly higher in stage 4 and 5 patients, compared with those in stage 3 (stage 3: 4.36 ± 0.49, stage 4: 4.50 ± 0.55, stage 5: 4.69 ± 0.73, mEq/L, \( p < 0.05 \)). Fig. 1). The ranges of the K⁺ levels of patients in this study were 3.87-4.85 meq/L in

| Table 1. Patient and Clinical Characteristics of Study Population (n = 531) |
|-----------------|-----------------|-----------------|
|                 | Stage 3 (n = 146) | Stage 4 (n = 170) | Stage 5 (n = 215) |
| Age, y          | 69.30 ± 12.91    | 68.16 ± 12.60    | 65.83 ± 12.74    |
| Male, No. (%)   | 99 (67.8%)       | 86 (50.6%)       | 95 (44.2%)       |
| BMI, kg/m²      | 26.11 ± 4.06     | 25.25 ± 3.82     | 26.24 ± 13.39    |
| Chronic GN, No. (%) | 18 (12.3%)      | 22 (12.9%)       | 51 (23.7%)       |
| Diabetes, No. (%) | 65 (44.5%)      | 98 (57.6%)       | 126 (58.6%)      |
| Hypertension, No. (%) | 122 (83.6%)  | 141 (82.9%)      | 180 (83.7%)      |
| Heart failure, No. (%) | 15 (10.3%)    | 18 (10.6%)       | 19 (8.8%)        |
| Coronary artery disease, No. (%) | 25 (17.1%) | 30 (17.6%)       | 25 (11.6%)       |
| CVA, No. (%)    | 13 (8.9%)        | 18 (10.6%)       | 25 (11.6%)       |
| Hyperlipidemia, No. (%) | 54 (37.0%)    | 49 (28.8%)       | 77 (35.8%)       |
| eGFR, Cockcroft-Gault, ml/min* | 36.83 ± 9.66 | 21.82 ± 6.45    | 9.84 ± 4.02      |
| eGFR, abbreviated MDRD, ml/min* | 39.75 ± 7.18  | 22.30 ± 4.74    | 8.91 ± 3.92      |
| Average K, meq/L* | 4.36 ± 0.49     | 4.50 ± 0.55      | 4.69 ± 0.73      |
| Hemoglobin, mg/dl* | 12.31 ± 2.07    | 10.69 ± 1.95     | 9.6 ± 1.56       |

**Abbreviations:** y: years; BMI: body mass index; GN: *glomerulonephritis; CVA: cerebral vascular attack; eGFR: estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease; K: potassium; *: Analysis of variance using least significant difference post hoc test (all stages compared with stage 3), \( p < 0.05 \).
CKD stage 3, 3.95-5.05 meq/L in CKD stage 4, and 3.96-5.42 meq/L in CKD stage 5. The hemoglobin levels became lower when renal function deteriorated (stage 3: 12.31 ± 2.07, stage 4: 10.69 ± 1.95, stage 5: 9.60 ± 1.56, g/dL, p < 0.05). We also found that there were more men and patients with hypertension, and diabetes mellitus in late stage CKD; however, the difference did not reach statistically significance (Table 1).

**Risk factors for hyperkalemia in CKD patients**

We performed multiple logistic regression analysis to evaluate the independent risk factors associated with hyperkalemia (Table 2). Age, gender and all covariates of significance in the univariate analysis were included for adjustment (i.e., diabetes mellitus, hypertension, eGFR, hemoglobin and use of ACEIs/ARBs). Male gender [Odds ratio (OR), 1.756; 95% confidential interval (CI), 1.164-2.649; p value = 0.008], diabetes mellitus (OR: 1.511; 95% CI, 1.043-2.191; p value = 0.009), the eGFR (OR: 0.967; 95% CI, 0.953-0.981; p value < 0.001), and the hemoglobin level (OR: 0.775; 95% CI, 0.692-0.867; p value < 0.001) remained significantly associated with the development of hyperkalemia.

**Use of ACEIs or ARBs and hyperkalemia in CKD patients**

In our study, more than 80% of stage 3 to 5 CKD patients had used ACEIs or ARBs for more than one year. Surprisingly, we did not find any association of usage of ACEIs/ARBs with hyperkalemia (Table 2).

To evaluate the effect of ACEIs/ARBs on the serum K+ level of patients with similar CKD stages, we compared the absolute serum K+ levels of the users and non-users of ACEIs/ARBs by CKD stage (Table 3). The additional analysis suggested that the serum K+ levels were not different between patients with or without ACEIs/ARBs in stage 3 to 5 CKD.

**Estimated K+ (eK+) level at different stages of CKD**

We had shown that high serum K+ levels were associated with worsening CKD stages. To demonstrate the degree of increment of serum potassium levels with progression of CKD, we plotted the serum K+ levels according to the related eGFR and a linear regression equation was obtained as eK+ = –0.0117 eGFR + 4.792 (Fig. 2). The equation sug-

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**Table 2. Multiple Logistic Regression Analysis Showing Risk Factors for Hyperkalemia in Patients in the Late Stages of CKD**

<table>
<thead>
<tr>
<th>Variable (incremental)</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1.756 (1.164-2.649)</td>
<td>0.008</td>
</tr>
<tr>
<td>Age</td>
<td>1.007 (0.992-1.023)</td>
<td>0.356</td>
</tr>
<tr>
<td>Diabetes (yes)</td>
<td>1.511 (1.043-2.191)</td>
<td>0.029</td>
</tr>
<tr>
<td>Hypertension (yes)</td>
<td>1.261 (0.797-1.997)</td>
<td>0.322</td>
</tr>
<tr>
<td>eGFR, MDRD, ml/min</td>
<td>0.967 (0.953-0.981)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.775 (0.692-0.867)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Use of ACEI/ARB</td>
<td>1.378 (0.836-2.262)</td>
<td>0.205</td>
</tr>
</tbody>
</table>

Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers.
Higher K⁺ level in advanced CKD

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Suggested a 0.117 mEq/L increase of serum K⁺ level per 10 eGFR (ml/min) decrease. We also observed that the standard deviation of the serum K⁺ levels became wider with more advanced CKD stages. We further plotted the standard deviation of the serum K⁺ levels according to the CKD stage (Fig. 3). For the estimated standard deviation of the serum K⁺ levels, the equation was “double the estimated standard deviation = 0.246 CKD stage + 0.198 with an R² of 0.9819”. All these results suggested that the mean serum potassium levels increased with a wider range of fluctuation as renal function deteriorated.

**DISCUSSION**

In the United States, hyperkalemia causes 5

defeases/1,000 person-years in patients with chronic kidney disease. However, it has been postulated that patients with end stage renal disease (ESRD) have a tolerance for hyperkalemia, and that the usual cardiac and neuromuscular sequelae of hyperkalemia are less evident in patients with ESRD than in those with normal renal function. We propose that the K⁺ level might increase in correlation with the deterioration of renal function within a range different from that of a patient with normal renal function without any clinical significance.

In patients with chronic renal insufficiency, the gradual elevation of the serum K⁺ level was thought to be an adaptive response. In our study, we also found that patients had higher average K⁺ levels when their renal function became worse (Table 1). Our patients did not have emergency electrocardiographic changes or muscle weakness even with high serum K⁺ levels (> 4.8 meq/L). Recognizing that

### Table 3. Potassium Level in Patients with and without ACEI/ARB

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>With ACEI/ARB, No (%)</th>
<th>Without ACEI/ARB, No (%)</th>
<th>Average K (meq/L) with ACEI/ARB</th>
<th>Average K (meq/L) without ACEI/ARB</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 3</td>
<td>121 (82.9%)</td>
<td>25 (17.1%)</td>
<td>4.34 ± 0.48</td>
<td>4.42 ± 0.55</td>
<td>0.46</td>
</tr>
<tr>
<td>Stage 4</td>
<td>144 (84.7%)</td>
<td>26 (15.3%)</td>
<td>4.50 ± 0.55</td>
<td>4.46 ± 0.56</td>
<td>0.72</td>
</tr>
<tr>
<td>Stage 5</td>
<td>178 (82.8%)</td>
<td>37 (17.2%)</td>
<td>4.70 ± 0.74</td>
<td>4.63 ± 0.72</td>
<td>0.60</td>
</tr>
</tbody>
</table>

**Abbreviation:** K: potassium; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers.

**p value** is for average K of the patient with and without ACEI/ARB.

**Fig. 2** The distribution of the average serum K⁺ Level correlated with the eGFR. The linear regression equation is shown, in which x = eGFR and y = the estimated potassium level of the eGFR. A trend of a higher potassium level is noted when the eGFR declines. Abbreviations used: MDRD: Modification of Diet in Renal Disease; eGFR: estimated glomerular filtration rate.

**Fig. 3** The range (standard deviation x 2) of the average serum K⁺ level in each stage of CKD. The linear regression equation is shown, in which x = CKD stage and y = the doubled value of the estimated standard deviation of the average serum K⁺ level. Abbreviation used: CKD: chronic kidney disease.
mild to moderate hyperkalemia might be an adaptive response is a clinically important issue which guides a clinician in determining the timing of the treatment of hyperkalemia. Insulin, β-agonists, sodium bicarbonate, and exchange resin might be given unnecessarily if the K+ level increase is in proportion with the progression of renal failure. The above therapies are not without complications. It is very important to know the proper K+ level in late stage CKD to avoid overtreatment of hyperkalemia.

Male gender, diabetes mellitus, low eGFR, and low hemoglobin were associated with the development of hyperkalemia in our cohort study (Table 2). The reason why male patients with CKD tend to have higher K+ level is unknown, and further research is needed to confirm this relationship. Our study demonstrated that a lower hemoglobin level was an independent risk factor for hyperkalemia even after adjustment for eGFR. All patients in the study came from a cohort of stable CKD patients at nephrology outpatient clinics, where they also participated in a multidisciplinary predialysis education program. Comorbidities and acute illnesses were recorded by a case-management nurse during medical visits. The case management nurse would then inform the physician of cases of severe illness, including those causing acute or chronic gastrointestinal blood loss. Patients with acute blood loss were usually admitted to the hospital or treated in an emergency department. For these reasons, the present study excluded most patients with severe bleeding; however, patients with occult bleeding may have been inadvertently included in the analysis.

Diabetic nephropathy is the single most common cause of ESRD in Taiwan, Europe, Japan, and the United States, with diabetic patients accounting for 25% to 45% of all patients enrolled in ESRD programs. Previous studies found that hyperkalemia appears to occur more frequently in patients with tubulointerstitial disease associated with diabetes mellitus and these patients tend to have hyporenin hypaldosteronism, which might be associated with high K+ levels and metabolic acidosis. In our study, multiple logistic regression analysis also showed diabetes mellitus was one of the independent risk factors associated with hyperkalemia. This result might come from the progressive increase in the diabetic population along with the progression of CKD in our study population.

ACEIs and ARBs are thought to have cardiorenal-protective benefits in CKD patients. ACEIs/ARBs are highly effective in reducing proteinuria and slowing progression to ESRD in nondiabetic nephropathy. Their effects on slowing decreases in the glomerular filtration rate are tightly linked to their antiproteinuric effects. It has been suggested that ACEIs/ARBs confer additional nephroprotection in diabetes beyond their effects on blood pressure. Therefore, the use of ACEIs/ARBs is often recommended as a first line treatment in CKD and diabetic nephropathy. Most of our CKD patients were taking ACEIs/ARBs. Hyperkalemia was thought to be a major complication in patients using ACEIs/ARBs; however, there was no significant difference in the serum K+ levels between patients using and not using ACEIs/ARBs (Table 3). Hyperkalemia seemed to have a stronger relation with a lower eGFR, than with usage of ACEIs/ARBs (Table 2). ACEIs/ARBs seemed to have no significant correlation with hyperkalemia in our CKD patients. It is unknown if hyperkalemia may develop in patients with concurrent intake of ACEIs/ARBs and diuretics or cations exchange resins, because most of these patients were excluded from our study.

To further confirm that the eGFR was the most significant determinant of the K+ level in CKD patients, we did a linear regression analysis of the serum K+ level against the eGFR (Fig. 2). We got a linear regression equation (y = –0.0117x + 4.792 in which x = eGFR and y = the estimated K+ level of the eGFR). This reflected that for every increase of 1 ml/min in the eGFR there was a decrease of 0.0117 meq/L in the serum K+ level from a base of 4.792 mEq/L. Nevertheless, the serum K+ level calculated from this equation was not comparable with the ranges of K+ levels which we observed in our CKD patients. On the other hand, the distribution of the serum K+ level, which was represented by the standard deviation of the average K+ level of the eGFR. The results reflected the fact that the kidney was less capable of keeping the serum K+ level within a narrow range as CKD progressed. This phenomenon might be clinically important when interpreting serum K+ levels in CKD patients.

In our study, the serum K+ level indeed increased when renal function deteriorated, but there were some limitations that influenced our results. The information on the assessment in K+ intake and
K+ excretion was limited in our study. Because all patients were enrolled in a predialysis education program and were counseled by the same dietitian, we presumed the differences in dietary K+ intake were minimal in our patients. We excluded patients with documented cardiac arrhythmias because hyperkalemia is particularly dangerous in these patients. Furthermore, we excluded use of certain drugs which could affect K+ renal handling, such as diuretics, β-blockers, digoxin, mineralocorticoids, and non-steroidal anti-inflammatory drugs. Therefore, we suggested that renal K+ excretion was approximately dependent on the renal function although it is also highly related with dietary K+. On the other hand, we did not take into consideration the acid-base status which might have influenced the K+ level in this study.

We found that the serum K+ level increased along with the decrease in the eGFR. ACEI / ARB usage was not significantly associated with the serum K+ level. The ranges of the serum K+ level in our patients may not represent the serum K+ levels of all individuals in the late stages of CKD. However, we still feel that interpretation of serum K+ should be adjusted in late stage CKD patients, although there is little in the literature concerning the appropriate range of the serum K+ level in these patients. Further randomized controlled studies are needed to determine the acceptable range of the K+ level for patients with advanced CKD.

**Acknowledgements**

The authors wish to express their deepest gratitude to all the patients who participated in this study.

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後期慢性腎臟病相關之高血鉀濃度

謝明芳 吳逸文 李進昌 王秀英 吳麥斯

背 景：血清中鉀離子濃度主要由腎臓維持在狹窄範圍內，但在不同程度的慢性腎臟病患者中，鉀離子濃度為多少並無定論。

方 法：我們設計一個橫斷面研究去觀察無臨床高血鉀症狀的後期慢性腎臟病患者之血清中平均鉀離子濃度。這 531 位後期慢性腎臟病的患者，自 2006 年三月開始追蹤至少一年，將病人依腎絲球濾過率 (MDRD eGFR) 分類至慢性腎臟病後期的三個階段，並記錄血清中肌酐酸、鉻離子濃度。

結 果：我們得到的數值反應出平均血鉀會隨著腎功能惡化而逐步上升，且男性、糖尿病、低腎絲球濾過率及低血色素皆可能是此研究中慢性腎臟病患者有高血鉀之危險因子；另外，當慢性腎臟病越嚴重時，平均血鉀的標準差會呈線性增加；在我們的研究中，使用 ACEI 或 ARB 與不同階段慢性腎臟病之高血鉀並無顯著關聯。

結 論：我們推測當腎絲球濾過率下降時，血中鉀離子會呈線性上升，尤其是慢性腎臟病第三階段之後；此外，男性、糖尿病及貧血可能是與慢性腎臟病患之血鉀升高相關的危險因子。而血清中鉀離子濃度的變化程度會隨著腎功能變差而變大。

(長庚醫誌 2011;34:418-25)

關鍵詞：慢性腎臟病，高血鉀

長庚醫療財團法人基隆長庚紀念醫院 腎臟科；長庚大學 醫學院

受文日期：民國99年5月27日; 接受刊載：民國99年12月22日

通訊作者：吳麥斯醫師，長庚醫療財團法人基隆長庚紀念醫院 腎臟科。基隆市204安樂區麥金路222號。

Tel.: (02)24313131 轉3169; Fax: (02)24335342; E-mail: maxwu1@cgmh.org.tw